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File 350:Derwent WPIX 1963-2006/UD,UM &UP=200643
         (c) 2006 The Thomson Corp.
File 347:JAPIO Dec 1976-2005/Dec(Updated 060404)
         (c) 2006 JPO & JAPIO
Set     Items   Description
S1       1252   IONTOPHORE? OR MICROIONTOPHORE?
S2     324250   TISSUE OR SKIN OR MUCOSA? ? OR CUTANEOUS? OR TRANSDERMAL?
S3    1413464   V OR VOLT OR VOLTS OR VOLTAGE? ?
S4     110111   PERCENT??? OR PER()CENT???
S5     174411   AC OR ALTERNATING()CURRENT
S6     827898   min OR mins OR MINUTE? ? OR hr OR HOUR OR HOURS OR HRS
S7     368904   BARRIER? ? OR STRATUM OR PERMEAT? OR PERMEAB?
S8    1622706   AGENT? ? OR ENHANCE? OR ENHANCING
S9     150606   FATTY()(ACID? ? OR ALCOHOL? ?) OR BILE()(ACID? ? OR SALT? -
             ?) OR (NONIONIC OR ANIONIC OR CATIONIC OR AMPHOTERIC)()SURFAC-
             TANT? ?
S10    918132   (ORGANIC OR HYDROCARBON)(1W)SOLVENT? ? OR ESTER? ? OR AMID-
             E? ? OR PYRROLIDONE? ? OR CYCLODEXTRIN? ?
S11    230211   SULFOXIDE? ? OR SULPHOXIDE? ? OR SULFATE? ? OR SULPHATE? ?
             OR SULFONATE? ? OR SULPHONATE? ?
S12   1634032   AZACYCLOALK?NONE? ? OR UREA OR TERPENE? ? OR ACID? ? OR AL-
             COHOL? ? OR DIOL? ? OR POLYOL? ?
S13     19061   FATTY()ETHER? ? OR LACTATE? ? OR MYRISTYL? ? OR PALMITATE?
             ? OR LINOLEATE? ?
S14       159   S1 AND S2 AND S3
S15         7   S1 AND S2 AND S5(S)S6
S16         7   S15 AND S7:S13
S17         1   S14 AND S3(S)S4
S18         0   S17 NOT S15
S19        85   S14 AND S7:S13
S20         0   IC=A61N001?
S21     36336   IC=A61F-002?
S22         0   S19 AND S20:S21
S23     28641   IC=A61N-001?
S24        57   S19 AND (S21 OR S23)
S25        53   S24 NOT S15
S26        27   S1/TI AND S25

 16/34/7     (Item 7 from file: 350)
DIALOG(R)File 350:Derwent WPIX
(c) 2006 The Thomson Corp. All rts. reserv.
011313166
WPI Acc No: 1997-291070/199727
  Iontophoretic delivery of medicaments through skin - with electrical
  treatment current between electrodes periodically reversed at very low
  frequencies to mitigate tissue damage
Patent Assignee: TAPPER R (TAPP-I)
Inventor: TAPPER R
Number of Countries: 014  Number of Patents: 004
Patent Family:
Patent No     Kind   Date     Applicat No    Kind   Date     Week
EP 776676      A2  19970604  EP 91118776     A   19911104  199727  B
                             EP 97101479     A   19911104
EP 776676      B1  20020227  EP 91118776     A   19911104  200215
                             EP 97101479     A   19911104
DE 69132943    E   20020404  DE 632943       A   19911104  200230
```

EP 97101479 A 19911104
ES 2169823 T3 20020716 EP 97101479 A 19911104 200256
Priority Applications (No Type Date): US 90607874 A 19901101
Cited Patents: 3.Jnl.Ref; EP 230153; EP 309093; EP 60452; EP 97436; GB 2206493; US 5006108
Patent Details:

| Patent No | Kind | Lan | Pg | Main IPC | Filing Notes |
|---|---|---|---|---|---|
| EP 776676 | A2 | E | 19 | A61N-001/30 | Div ex application EP 91118776 |
| | Designated States (Regional): AT BE CH DE DK ES FR GB GR IT LI LU NL SE | | | | |
| EP 776676 | B1 | E | | A61N-001/30 | Div ex application EP 91118776<br>Div ex patent EP 483883 |
| | Designated States (Regional): AT BE CH DE DK ES FR GB GR IT LI LU NL SE | | | | |
| DE 69132943 | E | | | A61N-001/30 | Based on patent EP 776676 |
| ES 2169823 | T3 | | | A61N-001/30 | Based on patent EP 776676 |

Abstract (Basic): EP 776676 A

An apparatus for the **iontophoretic** infusion of medical substances into a patient conducts electrical **current** through the **skin** from a first to a second electrode. The polarity of the electrodes is intermittently reversed at a frequency between 20 times per second and once every three **minutes**, causing simultaneous intermittent reversal of the **current** direction.

For the **iontophoretic** administration of drugs, e.g. lidocaine (claimed).

ADVANTAGE - The use of the apparatus mitigates **tissue** damage, enables long term dosimetry with single or multiple drugs of any polarity and at higher concentrations, and eliminates the need for buffering **agents** . The apparatus is relatively simple, economical and compact. It can deliver treatment substances with large and/or small molecular size and weight. It can be adjusted to control pH at the delivery site.

Dwg.0/6

Abstract (Equivalent): EP 483883 B

An apparatus (10) for applying **iontophoretic** treatment to a biological subject, said apparatus including means (15) for conducting an electrical **current** through a surface of said subject in a first direction from a first electrode (16a) to a second electrode (16b) on said subject, and also including means for reversing the polarity of said electrodes, said apparatus characterised by: the reversing means intermittently reversing, between approximately 20 times per second and approximately once every three **minutes** , the polarity of said electrodes to cause said electrical **current** to flow in a second direction opposite to said first direction thereby delivering an **AC current** of a frequency between 0.0027Hz and 10Hz which prevents **skin** damage, whereby **iontophoretic** treatment may be continuous for extended period of time.

Dwg.2/6

Derwent Class: A96; B07; P34; S05
International Patent Class (Main): A61N-001/30

**26/34/12 (Item 12 from file: 350)**
DIALOG(R)File 350:Derwent WPIX

013493115 **Image available**
WPI Acc No: 2000-665058/200064
**Iontophoresis device and current application method for administering prostagladins**

**to skin or mucous membrane in long-term controlled treatment of e.g. chronic arteriosclerosis with efficiency and drug storability**
Patent Assignee: HISAMITSU PHARM CO LTD (HISM )
Inventor: ADACHI H; HIGO N; KATAGAI K
Number of Countries: 025 Number of Patents: 008
Patent Family:

| Patent No | Kind | Date | Applicat No | Kind | Date | Week |
|---|---|---|---|---|---|---|
| WO 200061218 | A1 | 20001019 | WO 2000JP2234 | A | 20000406 | 200064 B |
| AU 200036714 | A | 20001114 | AU 200036714 | A | 20000406 | 200108 |
| EP 1170028 | A1 | 20020109 | EP 2000915378 | A | 20000406 | 200205 |
| | | | WO 2000JP2234 | A | 20000406 | |
| KR 2001109350 | A | 20011208 | KR 2001712991 | A | 20011012 | 200237 |
| JP 2000610549 | X | 20020716 | JP 2000610549 | A | 20000406 | 200261 |
| | | | WO 2000JP2234 | A | 20000406 | |
| US 6643544 | B1 | 20031104 | WO 2000JP2234 | A | 20000406 | 200374 |
| | | | US 2001958602 | A | 20011012 | |
| AU 769693 | B | 20040129 | AU 200036714 | A | 20000406 | 200412 |
| AU 769693 | B2 | 20040129 | AU 200036714 | A | 20000406 | 200454 |

Priority Applications (No Type Date): JP 99104576 A 19990412
Patent Details:

| Patent No | Kind | Lan | Pg | Main IPC | Filing Notes |
|---|---|---|---|---|---|
| WO 200061218 | A1 | J | 40 | A61N-001/30 | |
| Designated States (National): AU CA CN JP KR US | | | | | |
| Designated States (Regional): AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE | | | | | |
| AU 200036714 | A | | | A61N-001/30 | Based on patent WO 200061218 |
| EP 1170028 | A1 | E | | A61N-001/30 | Based on patent WO 200061218 |
| Designated States (Regional): AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE | | | | | |
| KR 2001109350 | A | | | A61N-001/30 | |
| JP 2000610549 | X | | | A61N-001/30 | Based on patent WO 200061218 |
| US 6643544 | B1 | | | A61N-001/30 | Based on patent WO 200061218 |
| AU 769693 | B | | | A61N-001/30 | Previous Publ. patent AU 200036714<br>Based on patent WO 200061218 |
| AU 769693 | B2 | | | A61N-001/30 | Previous Publ. patent AU 200036714<br>Based on patent WO 200061218 |

Abstract (Basic): WO 200061218 A1

NOVELTY - An **iontophoresis** device (I) for administering a prostaglandin to **skin** or mucous membrane, is new.

DETAILED DESCRIPTION - An **iontophoresis** device (I) for administering a prostaglandin to **skin** or mucous membrane comprises:

(a) a first electrode structural body containing the drug;

(b) a second electrode structural body; and

(c) a power supply electrically connected to both electrode structural bodies, with a stabilizing means to suppress hydrolysis of the prostaglandin while stored.

INDEPENDENT CLAIMS are also included for the following:

(1) a similar device to (I) in which the second electrode structural body also contains a prostaglandin;

(2) a **current** application method by electrically connecting the first and second electrode structural bodies while applying a pulsed direct-**current voltage** of 0.1-200 kHz; and

(3) another **current** application method in which the power supply of the device is a direct **current** and **the current application is carried out continuously for a total of 1-24 hrs**. by applying pulsed direct **current** or pulsed depolarized direct **current**.

USE - The device and **current** application method is for administering prostaglandins to **skin** or mucous membrane in long-term controlled treatment of chronic arteriosclerosis e.g. Buerger's disease and occlusive arteriosclerosis, vibration disease, progressive systemic sclerema and systemic erythematodes.

ADVANTAGE - Such device can provide high local efficiency and drug stability during storage for long-term controlled treatment.

DESCRIPTION OF DRAWING(S) - Structure of an **iontophoresis** device.
First electrode structural body (31)
second electrode structural body (32)
power supply (33)
pp; 40 DwgNo 3/5

Technology Focus:

TECHNOLOGY FOCUS - MECHANICAL ENGINEERING - Preferred Device: The stabilizing means is a drug-storing body to keep the prostaglandin at a dry state.

Preferred **Current** Application: The **current** application is continuously performed for 3-7 days/week.

PHARMACEUTICALS - Preferred Pharmaceutical: Particularly, a stabilizing **agent** or solubility- **enhancing agent** is added to effect chemical stabilization of the prostaglandin. At least some **surfactants** or water-soluble **cyclodextrins** are added to promote delivery of the prostaglandin.

Extension Abstract:

ADMINISTRATION - Administration is topical for **enhanced percutaneous** absorption.

EXAMPLE - To a gel (1 g) for carboxyvinyl polymer matrix (1 wt.% carboxyvinyl polymer with pH adjusted to 4 with 10-N sodium hydroxide) containing beta- **cyclodextrin** (100 mg) and some lactic **acid** was added prostaglandin E1 (250 mug) and then applied to the electrode structural body of an **iontophoresis** device for storage or application to **skin** at a constant **current** of 0.01 mA/cm2 for 4 hrs. Results of the study were: after storing at 60degreesC for 1 day, drug residual rate=85%; treatment effect=positive with no **skin** stimulation, and no polarity conversion.

Derwent Class: B07; J03; P34; S05
International Patent Class (Main): **A61N-001/30**

**26/34/17 (Item 17 from file: 350)**
DIALOG(R)File 350:Derwent WPIX

010571779 **Image available**
WPI Acc No: 1996-068732/199607
**Pulsed transport of substance through tissue using electrical pulse to cause electroporation - then using passive diffusion or iontophoresis with subsequent pulses applied after hours or even days**
Patent Assignee: CYGNUS THERAPEUTIC SYSTEMS (CYGN-N); CYGNUS INC (CYGN-N)
Inventor: BOMMANNAN D B; CHEN T; POTTS R O; WONG O
Number of Countries: 063 Number of Patents: 004
Patent Family:

| Patent No | Kind | Date | Applicat No | Kind | Date | Week | |
|---|---|---|---|---|---|---|---|
| WO 9600111 | A1 | 19960104 | WO 95US7951 | A | 19950623 | 199607 | B |
| AU 9529477 | A | 19960119 | AU 9529477 | A | 19950623 | 199616 | |
| EP 766579 | A1 | 19970409 | EP 95925294 | A | 19950623 | 199719 | |
| | | | WO 95US7951 | A | 19950623 | | |

JP 10511008 W 19981027 WO 95US7951 A 19950623 199902
JP 96503326 A 19950623
Priority Applications (No Type Date): US 94265306 A 19940624
Cited Patents: EP 625360; WO 9310854
Patent Details:
Patent No Kind Lan Pg Main IPC Filing Notes
WO 9600111 A1 E 33 A61N-001/30
Designated States (National): AM AT AU BB BG BR BY CA CH CN CZ DE DK EE ES FI GB GE HU IS JP KE KG KP KR KZ LK LR LT LU LV MD MG MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TT UA UG UZ VN
Designated States (Regional): AT BE CH DE DK ES FR GB GR IE IT KE LU MC MW NL OA PT SD SE SZ UG
AU 9529477 A A61N-001/30 Based on patent WO 9600111
EP 766579 A1 E A61N-001/30 Based on patent WO 9600111
Designated States (Regional): AT BE DE FR GB IE IT
JP 10511008 W 30 A61N-001/30 Based on patent WO 9600111
Abstract (Basic): WO 9600111 A

Pulsed transport of substance through **tissue** , partic. a drug through **skin** or artificial **tissue** , comprises applying an electrical pulse to cause electroporation, applying a driving force of longer duration than the pulse to force the substance through the **tissue** and repeating pulse application while the driving force is applied. The force is pref. passive diffusion and **iontophoresis** , most pref. the latter. The steps may be performed according to a schedule or pulse may be applied on demand or in response to a measured parameter. **Pulse strength is pref. 10-1000 V and duration 1 mus-50 ms.**

USE - The method can be used partic. for the administration of oestra**diol**, prog**esteron**e, demegestone, promegestone, testosterone and their **esters** , nitroglycerine and isosorbide nitrates, nicotine, chloropheniramine, terfenadine, triprolidine, hydrocortisone, oxicam derivs., such as piroxicam, ketoprofen, thiomucase, buprenorphine, fentanyl and its analogues, naloxone, codeine, dihydroergotamine, pizotiline, salbutamol, terbutaline, misoprostol, emprostil, omeprazole, imipramine, **metoclopramide** , scopolamine, growth releasing factor, somatostatin, clonidine, nifedipine, verapamil, ephedrine, propranolol, metoprolol, spironolactone, hydrochlorothiazide, flunarizine, molsidomine, heparin fractions, salts of **acids** and bases, salmon calcitonin, neurotensin, enzymes, vitamins, nutrients, DNA or RNA.

ADVANTAGE - The method keeps the **skin permeability** high over an extended period of time, with repeat pulses applied **hours** or days later for more efficient administration with min. **skin** damage.

Dwg.7/8

Derwent Class: B07; P34
International Patent Class (Main): **A61N-001/30**

**26/34/18 (Item 18 from file: 350)**
DIALOG(R)File 350:Derwent WPIX
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010292045 **Image available**
WPI Acc No: 1995-193304/199525
**Reducing hydrolysis of water in iontophoretic electrodes for transdermal drug delivery - by incorporating ionic drug with negatively charged counter-ion in reservoir, applying to electroconductive member, applying to skin of patient, and applying voltage**

Patent Assignee: ALZA CORP (ALZA )
Inventor: LATTIN G A; PHIPPS J B; UNTEREKER D F
Number of Countries: 001 Number of Patents: 001
Patent Family:

| Patent No | Kind | Date | Applicat No | Kind | Date | Week |
|---|---|---|---|---|---|---|
| US 5415628 | A | 19950516 | US 84665698 | A | 19841029 | 199525 B |
| | | | US 84665699 | A | 19841029 | |
| | | | US 88154566 | A | 19880210 | |
| | | | US 92891319 | A | 19920529 | |
| | | | US 93101803 | A | 19930802 | |

Priority Applications (No Type Date): US 88154566 A 19880210; US 84665698 A 19841029; US 84665699 A 19841029; US 92891319 A 19920529; US 93101803 A 19930802
Patent Details:

| Patent No | Kind | Lan | Pg | Main IPC | Filing Notes |
|---|---|---|---|---|---|
| US 5415628 | A | | 14 | A61N-001/30 | CIP of application US 84665698 |
| | | | | | CIP of application US 84665699 |
| | | | | | Div ex application US 88154566 |
| | | | | | Cont of application US 92891319 |
| | | | | | CIP of patent US 4747819 |
| | | | | | CIP of patent US 4774787 |
| | | | | | Div ex patent US 5135477 |

Abstract (Basic): US 5415628 A

Reducing hydrolysis of water in an **iontophoretic** electrode for delivery of an ionic drug having a positive charge, comprises: (a) incorporating the ionic drug with a negatively charged counter-ion into a reservoir through which the ionic drug is **permeable** ; (b) applying to the reservoir an electroconductive member comprising an intercalation cpd contg. alkali metal capable of being readily oxidised and releasing the alkali metal when a positive **voltage** is applied to the conductive member; after the incorporating step, and (c) applying the reservoir to the **skin** of a patient.

While the reservoir is applied to the **skin** of the patient and the conductive member is applied to the reservoir, a positive **voltage** is applied to the conductive member to oxidise the alkali metal and to drive the ionic drug through the **skin** of the patient.

Also claimed are methods where (c) involves applying a negative **voltage** to the conductive member to absorb the ionic alkali metal and to drive the ionic drug through the **skin** of the patient.

USE - The method is useful in **iontophoretic** drug delivery.

ADVANTAGE - Electrolysis of water is reduced.

Dwg.1/4

Derwent Class: B07; P34; S05
International Patent Class (Main): **A61N-001/30**

**26/34/19 (Item 19 from file: 350)**
DIALOG(R)File 350:Derwent WPIX

009782126
WPI Acc No: 1994-061979/199408
**Drug absorption accelerator for iontophoresis - comprises electrolyte, ethanol@, water and monoterpene analogue and/or fatty acid monoglyceride**
Patent Assignee: ADVANCE KK (ADVN ); JAPAN TOBACCO INC (NISB )
Number of Countries: 001 Number of Patents: 001
Patent Family:

Patent No Kind Date Applicat No Kind Date Week
JP 6016538 A 19940125 JP 92198949 A 19920703 199408 B
Priority Applications (No Type Date): JP 92198949 A 19920703
Patent Details:
Patent No Kind Lan Pg Main IPC Filing Notes
JP 6016538 A 7 A61K-009/08
Abstract (Basic): JP 6016538 A

Drug absorption accelerating compsn. for **iontophoresis** comprises electrolyte having sufficient electro conductivity, 10-70 wt % of ethanol, absorption accelerator consisting of 0.5-20 wt% of **monoterpene** analogue and/or **fatty acid** mono-glyceride, and water.

Ph of the compsn. is pref. 3-7. **Fatty acid** monoglyceride is pref. glycerol **monoester** of 6-12C medium chain **fatty acid** , e.g. caproic **acid** monoglyceride, caprylic **acid** monoglyceride, capric **acid** monoglyceride and lauric **acid** monoglyceride.

Examples of **monoterpene** analogue as absorption accelerator are 1-menthol, limonene and cineole. The ratio of absorption accelerator is pref. 0.5-20 wt%. Examples of electrolyte are NaCl, Na2CO3, and Na2HPO4 and citric **acid** . The ratio of electrolyte is 0.1-10 wt%. Examples of polypeptide-type drug are calcitonin, adrenocorticotropic hormone (ACTH), parathyroid hormone (PTH), insulin, secretin, oxytocin, angiotensin, beta-endorphin, glucagon, vasopressin, LH-RH, enkephalin, etc.

USE/ADVANTAGE - The compsn. aids absorption of polypeptide-type drug effectively through the **skin** even under low electric currency and **low voltage** . The polypeptide-type drug can be administered per**cutaneous**ly not in a form of injection or oral admin., avoiding pain and disorder in digestive organs.

Dwg.0/1

Derwent Class: B05; P34
International Patent Class (Main): A61K-009/08
International Patent Class (Additional): A61K-037/02; A61K-047/10; A61K-047/14; **A61N-001/30**

**26/34/21 (Item 21 from file: 350)**
DIALOG(R)File 350:Derwent WPIX
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009503238 **Image available**
WPI Acc No: 1993-196774/199324

**Iontophoretic device for delivering drug through skin of patient - uses high energy batteries switched selectively to operate in series or parallel according to status of skin resistance**

Patent Assignee: ALZA CORP (ALZA )
Inventor: BADZINSKI J D; HAAK R P; MCNICHOLS L A; MC NICHOLS L A
Number of Countries: 026 Number of Patents: 012
Patent Family:
Patent No Kind Date Applicat No Kind Date Week
WO 9310854 A1 19930610 WO 92US10419 A 19921203 199324 B
ZA 9209386 A 19930825 ZA 929386 A 19921203 199340
AU 9332357 A 19930628 AU 9332357 A 19921203 199342
EP 615461 A1 19940921 WO 92US10419 A 19921203 199436
EP 93900816 A 19921203
US 5374242 A 19941220 US 91802080 A 19911203 199505
US 93164663 A 19931207
JP 7501468 W 19950216 WO 92US10419 A 19921203 199516

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | JP 93510342 | A | 19921203 | | |
| EP 615461 | B1 | 19960925 | WO 92US10419 | A | 19921203 | 199643 | |
| | | | EP 93900816 | A | 19921203 | | |
| DE 69214158 | E | 19961031 | DE 92614158 | A | 19921203 | 199649 | |
| | | | WO 92US10419 | A | 19921203 | | |
| | | | EP 93900816 | A | 19921203 | | |
| CA 2121372 | C | 20030204 | CA 2121372 | A | 19921203 | 200318 | |
| | | | WO 92US10419 | A | 19921203 | | |
| JP 2003038661 | A | 20030212 | JP 93510342 | A | 19921203 | 200321 | |
| | | | JP 2002209493 | A | 19921203 | | |
| JP 3424753 | B2 | 20030707 | WO 92US10419 | A | 19921203 | 200345 | |
| | | | JP 93510342 | A | 19921203 | | |
| JP 3779240 | B2 | 20060524 | JP 93510342 | A | 19921203 | 200635 | |
| | | | JP 2002209493 | A | 20020718 | | |

Priority Applications (No Type Date): US 91802080 A 19911203; US 93164663 A 19931207
Cited Patents: EP 92015; WO 8607268; WO 9115258
Patent Details:

| Patent No | Kind | Lan | Pg | Main IPC | Filing Notes |
|---|---|---|---|---|---|
| WO 9310854 | A1 | E | 21 | A61N-001/30 | |
| Designated States (National): AU CA FI JP KR NO NZ | | | | | |
| Designated States (Regional): AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE | | | | | |
| ZA 9209386 | A | | 26 | A61N-000/00 | |
| AU 9332357 | A | | | A61N-001/30 | Based on patent WO 9310854 |
| EP 615461 | A1 | E | 21 | A61N-001/30 | Based on patent WO 9310854 |
| Designated States (Regional): AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE | | | | | |
| US 5374242 | A | | 11 | A61N-001/30 | Cont of application US 91802080 |
| JP 7501468 | W | | 1 | A61N-001/30 | Based on patent WO 9310854 |
| EP 615461 | B1 | E | 14 | A61N-001/30 | Based on patent WO 9310854 |
| Designated States (Regional): AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE | | | | | |
| DE 69214158 | E | | | A61N-001/30 | Based on patent EP 615461 |
| | | | | | Based on patent WO 9310854 |
| CA 2121372 | C | E | | A61N-001/30 | Based on patent WO 9310854 |
| JP 2003038661 | A | | 10 | A61N-001/30 | Div ex application JP 93510342 |
| JP 3424753 | B2 | | 9 | A61N-001/30 | Previous Publ. patent JP 7501468 |
| | | | | | Based on patent WO 9310854 |
| JP 3779240 | B2 | | 13 | A61N-001/30 | Div ex application JP 93510342 |
| | | | | | Previous Publ. patent JP 2003038661 |

Abstract (Basic): WO 9310854 A

The **iontophoretic** device includes a power supply (21) including batteries and control circuitry, and donor electrode and return electrode assemblies (18,19) separated electrically and physically by an insulator (26). The donor electrode (22) consists of a conductive matrix that serves to couple the power supply to a reservoir (24) containing an ionisable supply of the drug to be administered.

The power supply causes an electrical potential difference between donor and return electrodes while the body of the patient provides a conductive pathway. Under the influence of the **voltage** , ions of the beneficial drug are transported out of the reservoir and through the ion-conducting adhesive layer (27) adhering to the patient's **skin** .

USE/ADVANTAGE - Controlled delivery of drugs, peptides, polypeptides, proteins and other macromolecules. Provides different arrangements for connecting **voltage** source within a system.

Dwg.2/5
Abstract (Equivalent): EP 615461 B
An **iontophoretic** delivery system for delivering a beneficial **agent** through an intact body surface of a patient by **iontophoresis**, the system including a first electrode means (18) for containing a beneficial **agent** to be delivered and for contacting a body surface of a patient in **agent** -transmitting relation therewith, a second electrode means (19) for contacting the body surface in ion-transmitting relation therewith at a location spaced apart from the first electrode means, at least two electrical power sources (36, 38) electrically connected to the first and second electrode means (18, 19), each power source (36, 38) producing an electrical potential difference, the system being characterised by bi-state switch means (30, 32, 34) for said two power sources (36, 38) and said first and second electrode means (18, 19) for selectively switching between: (1) a first state in which said two power sources are connected in series circuit relation between said first and second electrode means, and (2) a second state in which said two power sources are connected in parallel circuit relation between said first and second electrode means.
(Dwg.1/5
Abstract (Equivalent): US 5374242 A
The **iontophoretic** delivery feed for delivering a beneficial **agent** by **iontophoresis** through an intact body surface of a patient having an associated body surface electrical resistance comprises a first electrode for containing a beneficial **agent** to be delivered and for contacting a body surface of a patient in **agent** -transmitting relation.
A second electrode contacts the body surface in ion-transmitting relation at a location spaced apart from the first electrode. There are first and second electrical power sources, each having a pair of terminals and each producing an electrical potential difference between its pair of terminals. A bi-state switch is coupled to the two power sources and first and second electrodes.
USE/ADVANTAGE - The **iontophoretic** device is for **transdermally** or trans**mucosa**lly delivering a beneficial **agent** to a patient. More particularly, to an electrically powered **iontophoretic** delivery device having an improved power supply.
Dwg.2/5
Derwent Class: P34; S05
International Patent Class (Main): A61N-000/00; **A61N-001/30**
International Patent Class (Additional): A61M-037/00

**16/26,TI/5 (Item 5 from file: 350)**
DIALOG(R)File 350:Derwent WPIX
(c) 2006 The Thomson Corp. All rts. reserv.
014073418
WPI Acc No: 2001-557631/200162
**Extracting substance from body through tissue , involves applying electrical signals comprising AC signal to tissue , and adjusting signal to maintain constant electrical state within region of tissue**

**16/26,TI/6 (Item 6 from file: 350)**
DIALOG(R)File 350:Derwent WPIX
(c) 2006 The Thomson Corp. All rts. reserv.

013607000
WPI Acc No: 2001-091208/200110
**Skin compatible hot-melt processable, pressure-sensitive adhesive used in biomedical electrodes and pharmaceutical delivery devices**

**26/26,TI/1 (Item 1 from file: 350)**
DIALOG(R)File 350:Derwent WPIX
(c) 2006 The Thomson Corp. All rts. reserv.
017071316
WPI Acc No: 2005-395657/200540
**Vaccine delivery system for delivering, e.g. flu vaccines, includes agent formulation containing vaccine, non-electroactive microprojection member having stratum corneum-piercing microprojections, and iontophoresis device**

**26/26,TI/2 (Item 2 from file: 350)**
DIALOG(R)File 350:Derwent WPIX
(c) 2006 The Thomson Corp. All rts. reserv.
016636044
WPI Acc No: 2004-794757/200478
**Iontophoretic transdermal delivery system used as e.g. single bandage, comprises first and second reservoirs for containing therapeutic agents, self-contained power source, and first and second electrodes for ionizing the therapeutic agents**

**26/26,TI/3 (Item 3 from file: 350)**
DIALOG(R)File 350:Derwent WPIX
(c) 2006 The Thomson Corp. All rts. reserv.
016403381
WPI Acc No: 2004-561292/200454
**Iontophoretic transdermal delivery system for delivering therapeutic agents into user's skin, comprises first and second ends including respective reservoir, and connecting portion housing self-contained power source and two electrodes**

**26/26,TI/6 (Item 6 from file: 350)**
DIALOG(R)File 350:Derwent WPIX
(c) 2006 The Thomson Corp. All rts. reserv.
015874956
WPI Acc No: 2004-032787/200403
**Compound iontophoretically transporting-device includes reference electrode in conjunction with at least one of two iontophoretic electrodes to monitor and control electrical resistance of body tissue at localized region**

**26/26,TI/7 (Item 7 from file: 350)**
DIALOG(R)File 350:Derwent WPIX
(c) 2006 The Thomson Corp. All rts. reserv.
015646258
WPI Acc No: 2003-708441/200367
**Enhancing transcutaneous flux rate of active permeant into body surface, involves simultaneous application of active permeant with sonophoresis, iontophoresis , electroporation, mechanical vibrations and magnetophoresis**

**26/26,TI/9 (Item 9 from file: 350)**
DIALOG(R)File 350:Derwent WPIX
(c) 2006 The Thomson Corp. All rts. reserv.
014234627
WPI Acc No: 2002-055325/200207
**Method for transdermal administration of ascorbic acid utilizes iontophoresis with**

**metal phosphate salt of ascorbic acid for treatment of cosmetic skin disorders**

**26/26,TI/10 (Item 10 from file: 350)**
DIALOG(R)File 350:Derwent WPIX
(c) 2006 The Thomson Corp. All rts. reserv.
014037866
WPI Acc No: 2001-522079/200157
**Transdermal iontophoretic therapeutic agent delivery system, comprises several self-contained serially connected galvanic sources**

**26/26,TI/11 (Item 11 from file: 350)**
DIALOG(R)File 350:Derwent WPIX
(c) 2006 The Thomson Corp. All rts. reserv.
013539046
WPI Acc No: 2001-023252/200103
**Preparation of salicylate and insulin is driven iontophoretically into surface**

**26/26,TI/13 (Item 13 from file: 350)**
DIALOG(R)File 350:Derwent WPIX
(c) 2006 The Thomson Corp. All rts. reserv.
012440080
WPI Acc No: 1999-246188/199921
**Iontophoretic drug delivery device**

**26/26,TI/14 (Item 14 from file: 350)**
DIALOG(R)File 350:Derwent WPIX
(c) 2006 The Thomson Corp. All rts. reserv.
011669687
WPI Acc No: 1998-086596/199808
**Iontophoresis device for non-invasively administering alpha-v beta-3 integrin antagonist - comprises current distributing member, agent reservoir containing ionised or ionisable integrin antagonist, electrolyte reservoir and power source**

**26/26,TI/15 (Item 15 from file: 350)**
DIALOG(R)File 350:Derwent WPIX
(c) 2006 The Thomson Corp. All rts. reserv.
010865529
WPI Acc No: 1996-362480/199636
**Iontophoresis device for transcutaneous admin. of antithrombotic, anticoagulant or antiinflammatory anionic glucosaminoglycan - comprises negative electrode in contact with reservoir contg. active ingredient, positive electrode and electric generator**

**26/26,TI/16 (Item 16 from file: 350)**
DIALOG(R)File 350:Derwent WPIX
(c) 2006 The Thomson Corp. All rts. reserv.
010677798
WPI Acc No: 1996-174753/199618
**Iontophoretic device, useful for drug admin. - includes drug-storing layer, electric transfer element with electroconductive adhesive layer, and non-transfer element etc**

**26/26,TI/20 (Item 20 from file: 350)**
DIALOG(R)File 350:Derwent WPIX
(c) 2006 The Thomson Corp. All rts. reserv.
009684822

WPI Acc No: 1993-378376/199348
**Appts. for iontophoretic application of active agents - comprising electrode, counter electrode, and appts. for supplying current connected to both electrodes**

**26/26,TI/22 (Item 22 from file: 350)**
DIALOG(R)File 350:Derwent WPIX
(c) 2006 The Thomson Corp. All rts. reserv.
009156317
WPI Acc No: 1992-283761/199234
**Increased efficiency iontophoretic drug delivery - uses electrode of sacrificial** material to oxidise counter-ions forming immo**bile** cpd

**26/26,TI/23 (Item 23 from file: 350)**
DIALOG(R)File 350:Derwent WPIX
(c) 2006 The Thomson Corp. All rts. reserv.
009056054
WPI Acc No: 1992-183444/199222
**Iontophoretic drug delivery device - with reservoir matrix hydrated immediately prior to use pref. by rupturing liquid-containing capsules**

**26/26,TI/24 (Item 24 from file: 350)**
DIALOG(R)File 350:Derwent WPIX
(c) 2006 The Thomson Corp. All rts. reserv.
008703876
WPI Acc No: 1991-207896/199128
**Iontophoretic drug delivery - through skin on back, used for transdermal admin. of e.g.** metoclopra**mide**

**26/26,TI/25 (Item 25 from file: 350)**
DIALOG(R)File 350:Derwent WPIX
(c) 2006 The Thomson Corp. All rts. reserv.
008644514
WPI Acc No: 1991-148544/199120
**Iontophoresis device epidermally administering drug - includes rate controlling membrane only permeable to drug when voltage is applied**

**26/26,TI/26 (Item 26 from file: 350)**
DIALOG(R)File 350:Derwent WPIX
(c) 2006 The Thomson Corp. All rts. reserv.
008260744
WPI Acc No: 1990-147745/199019
**Membrane for iontophoretic agent delivery device - in which prevents passive release of drug with release of drug controlled by electric current**

**26/26,TI/27 (Item 27 from file: 350)**
DIALOG(R)File 350:Derwent WPIX
(c) 2006 The Thomson Corp. All rts. reserv.
007038228
WPI Acc No: 1987-038225/198706
**Iontophoretic device for delivering kojic acid under skin - comprising impregnated working electrode, dispersive electrode** and **oscillator**

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File 155:MEDLINE(R) 1950-2006/Jul 06
         (c) format only 2006 Dialog
File   5:Biosis Previews(R) 1969-2006/Jul W1
         (c) 2006 The Thomson Corporation
File  71:ELSEVIER BIOBASE 1994-2006/Jul W1
         (c) 2006  Elsevier Science B.V.
File  73:EMBASE 1974-2006/Jul 07
         (c) 2006 Elsevier Science B.V.
File  94:JICST-EPlus 1985-2006/Apr W1
         (c)2006 Japan Science and Tech Corp(JST)
File 144:Pascal 1973-2006/Jun W2
         (c) 2006 INIST/CNRS
File  34:SciSearch(R) Cited Ref Sci 1990-2006/Jul W1
         (c) 2006 Inst for Sci Info
File 434:SciSearch(R) Cited Ref Sci 1974-1989/Dec
         (c) 1998 Inst for Sci Info
File 156:ToxFile 1965-2006/Jul W1
         (c) format only 2006 Dialog
Set     Items   Description
S1      37317   IONTOPHORE? OR MICROIONTOPHORE?
S2    6825398   TISSUE OR SKIN OR MUCOSA? ? OR CUTANEOUS? OR TRANSDERMAL?
S3    3492943   V OR VOLT OR VOLTS OR VOLTAGE? ?
S4    1651896   PERCENT??? OR PER()CENT???
S5     190542   ac OR ALTERNATING()CURRENT
S6    3750514   min OR mins OR minUTE? ? OR hr OR HOUR OR HOURS OR HRS
S7       1608   S1 AND S2 AND S3
S8         52   S7 AND S5
S9         11   S8 AND (S4 OR S6)
S10         7   RD  (unique items) [not relevant]
S11   1280868   BARRIER? ? OR STRATUM OR PERMEAT? OR PERMEAB?
S12   9785040   AGENT? ? OR ENHANCE? OR ENHANCING OR MODIFY??? OR MODIFIE?
            ? OR MODIFICATION
S13   8383428   CHANGE? ? OR CHANGING OR ALTER????
S14    860383   FATTY()(ACID? ? OR ALCOHOL? ?) OR BILE()(ACID? ? OR SALT? -
            ?) OR (NONIONIC OR ANIONIC OR CATIONIC OR AMPHOTERIC)()SURFAC-
            TANT? ?
S15   1354837   (ORGANIC OR HYDROCARBON)(1W)SOLVENT? ? OR ESTER? ? OR AMID-
            E? ? OR PYRROLIDONE? ? OR CYCLODEXTRIN? ?
S16   1003835   SULFOXIDE? ? OR SULPHOXIDE? ? OR SULFATE? ? OR SULPHATE? ?
           OR SULFONATE? ? OR SULPHONATE? ?
S17   9491514   AZACYCLOALK?NONE? ? OR UREA OR TERPENE? ? OR ACID? ? OR AL-
            COHOL? ? OR DIOL? ? OR POLYOL? ?
S18    397777   FATTY()ETHER? ? OR LACTATE? ? OR MYRISTYL? ? OR PALMITATE?
            ? OR LINOLEATE? ?
S19       101   S1 AND S2 AND S5
S20     25892   S11(2N)S12
S21     40992   S11(3N)S13
S22   3375505   S14:S16 OR S18
S23       281   (S7 OR S19) AND S20:S22
S24       465   (S7 OR S19) AND S17
S25       145   S23:S24 AND (S4 OR S6)
S26        75   RD  (unique items)
S27         7   S26/2002
S28         4   S26/2003
S29         2   S26/2004
S30         3   S26/2005
```

S31 1 S26/2006
**S32 7 S26/2001**
S33 51 S26 NOT S27:S32
S34 31 S1/TI,DE AND S33
**S35 31 Sort S34/ALL/PY,A**
S36 19 S33 NOT (S34 OR S9)
**S37 19 Sort S36/ALL/PY,A**

**32/6/7 (Item 2 from file: 34)**
09318018 Genuine Article#: 392PF Number of References: 37
**Title: Capillary recruitment is impaired in essential hypertension and relates to insulin's metabolic and vascular actions** (ABSTRACT AVAILABLE)
Publication date: 20010100

**32/7/5 (Item 4 from file: 73)**
DIALOG(R)File 73:EMBASE
(c) 2006 Elsevier Science B.V. All rts. reserv.
11058151 EMBASE No: 2001062258
**Buccal iontophoretic delivery of atenolol.HCl employing a new in vitro three-chamber permeation cell**
Jacobsen J.
J. Jacobsen, Department of Pharmaceutics, Royal Danish School of Pharmacy, Universitetsparken 2, DK-2100 Copenhagen O Denmark
AUTHOR EMAIL: jeja@dfh.dk
Journal of Controlled Release ( J. CONTROL. RELEASE ) (Netherlands) 29 JAN 2001, 70/1-2 (83-95)
CODEN: JCREE ISSN: 0168-3659
PUBLISHER ITEM IDENTIFIER: S016836590000328X
DOCUMENT TYPE: Journal ; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 19
The present work showed that the **iontophoretic** approach was feasible to **enhance** buccal drug delivery. A new in vitro horizontal three-chamber **iontophoretic permeation** cell has been developed to reflect the in vivo **iontophoretic** drug delivery more closely, electrodes were positioned on the epithelial side in separate chambers. **Iontophoretic** delivery of atenolol.HCl across porcine buccal **mucosa** increased proportional to (a) increased initial donor concentration in the range of 0.027 M to 0.10 M atenolol.HCl, (b) increased "on time" of **current** on/off ratio valued 50/50, 75/25 and 90/10 resulting in **enhancement** ratios 19, 58, and 112 respectively, initially applying 0.10 M atenolol.HCl and (c) increased **current** density valued 0.1, 0.2, 0.3, and 0.4 mA/cmSUP2 obtaining **enhancement** ratios 6, 18, 36, and 58 respectively, initially applying 0.10 M atenolol.HCl. Microscopy of hematoxyilin-eosin stained sections of porcine buccal **mucosae** conducting 8-h passive **permeation** showed minute morphological **alterations** whereas 8-h **iontophoretic** treatment showed disordering of the outer epithelial cell layers, **alterations** being more pronounced in **mucosae** from reference chambers than donor chambers. The results demonstrated the feasibility of the **iontophoretic** approach to **enhance** and control the rate of buccal drug delivery, hence the usefulness of the new **permeation** cell. (c) 2001 Elsevier Science B. **V.**

**35/6/1 (Item 1 from file: 155)**
06430354 PMID: 6146369

**Endplate blocking actions of lophotoxin.**
Jul 1984

**35/6/2 (Item 2 from file: 155)**
07805606 PMID: 2902201
**An iontophoretic study of single somatosensory neurons in rat granular cortex serving the limbs: a laminar analysis of glutamate and acetylcholine effects on receptive-field properties.**
Aug 1988

**35/6/5 (Item 5 from file: 155)**
09617611 PMID: 7682858
**L-NAME blocks responses to NMDA, substance P and noxious cutaneous stimuli in cat dorsal horn.**
Mar 1993

**35/6/6 (Item 6 from file: 73)**
05639373 EMBASE No: 1994045123
**Inhibition of protein kinase C differentially affects baroreflex inhibition and hypoxic excitation of medullary vasomotor neurons in rats**
1994

**35/6/9 (Item 9 from file: 73)**
06321722 EMBASE No: 1995358621
**NMDA and non-NMDA receptors mediate taste afferent inputs to cortical taste neurons in rats**
1995

**35/6/10 (Item 10 from file: 73)**
06727759 EMBASE No: 1997009221
**Effects of N- and L-type calcium channel antagonists on the responses of nociceptive spinal cord neurons to mechanical stimulation of the normal and the inflamed knee joint**
1996

**35/6/11 (Item 11 from file: 94)**
02690560 JICST ACCESSION NUMBER: 96A0228206 FILE SEGMENT: JICST-E
**Eveluation of iontophoretic transdermal deliverv for the treatment of keloids and hypertrophic scars. Using triamcinolone acetonide and tranilast.**, 1996

**35/6/12 (Item 12 from file: 155)**
11061093 PMID: 8885011
**Transdermal iontophoretic delivery of triamcinolone acetonide: a preliminary study in hairless rats.**
Sep 1996

**35/6/13 (Item 13 from file: 73)**
06802512 EMBASE No: 1997084997
**Inhibition of dopamine re-uptake: Significance for** nigraldopamine neuron **activity**
1997

**35/6/19 (Item 19 from file: 155)**
11346564 PMID: 9165536
**Macromolecules as novel transdermal transport enhancers for skin electroporation.**
May 1997

**35/6/20 (Item 20 from file: 155)**
11320166 PMID: 9133582
**Monitoring cellular edema at single-neuron level by electrical resistance measurements.**
Apr 4 1997

**35/6/21 (Item 21 from file: 73)**
07140883 EMBASE No: 1998029824
**Transdermal delivery of cyclosporin-A using electroporation**
02 JAN 1998

**35/6/26 (Item 26 from file: 71)**
01305734 1999023609
**In vivo efficacy and safety of skin electroporation**

**35/6/27 (Item 27 from file: 73)**
10758682 EMBASE No: 2000234947
**Nicotine inhibits firing activity of dorsal raphe 5-HT neurones in vivo**
2000

**35/6/28 (Item 28 from file: 73)**
10712098 EMBASE No: 2000200974
**Interactions of glutamate receptor agonists with long-term potentiation in the rat hippocampal slice**
23 JUN 2000

**35/6/29 (Item 29 from file: 144)**
14730965 PASCAL No.: 00-0407344
**Enhanced transdermal delivery of tetracaine by electroporation**
2000

**35/6/30 (Item 30 from file: 155)**
12942686 PMID: 11086923
**Effects of application voltage and cathode and anode positions at electroporation on the in vitro permeation of benzoic acid through hairless rat skin.**
Nov 2000

**35/7/3 (Item 3 from file: 155)**
DIALOG(R)File 155:MEDLINE(R)

08451795 PMID: 2339093
**Transport mechanisms in iontophoresis . III. An experimental study of the contributions of electroosmotic flow and permeability change in transport of low and high molecular weight solutes.**
Pikal M J; Shah S
Lilly Research Laboratories, Eli Lilly and Co., Indianapolis, Indiana 46285.
Pharmaceutical research (UNITED STATES) Mar 1990, 7 (3) p222-9, ISSN 0724-8741--Print Journal Code: 8406521
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM

Record type: MEDLINE; Completed

The objective of this research was to provide in vitro transport data designed to clarify the relative importance of **permeab**ility increase and electroosmotic flow in flux **enhanc**ement via **iontophoresis** . **Iontophoretic** fluxes were measured with both anode and cathode donor cells, and passive fluxes were measured both before **iontophoresis** (Passive 1) and after **iontophoresis** (Passive 2). Data were generated for three uncharged low molecular weight solutes (glycine, glucose, and tyrosine) and two high molecular weight anionic species (carboxy inulin and bovine serum albumin). Flux **enhanc**ement is greater for anodic delivery than for cathodic delivery, even for the negatively charged molecules, and anodic flux of glucose decreases as the concentration of NaCl increases. Both observations are consistent with a mass transfer mechanism strongly dependent on electroosmotic flow. Steady-state anodic flux at 0.32 mA/cm2, expressed as equivalent donor solution flux (in microliters/ **hr** cm2), ranged from 6.1 for glycine to about 2 for the large anions. As expected, **iontophoretic** flux is higher at 3.2 mA/cm2 than at 0.32 mA/cm2, and passive flux measured after **iontophoresis** is about a factor of 10 greater than the corresponding flux measured before the **skin** was exposed to electric **current**. There are two mechanisms for flux **enhanc**ement relative to passive flux on "fresh" hairless mouse **skin** : (1) the effect of the **voltage** in increasing mass transfer over the passive diffusion level, the effect of electroosmotic flow dominating this contribution in the systems studied in this report; and (2) the effect of prior **current** flow in increasing the "intrinsic **permeab**ility" of the **skin** .(ABSTRACT TRUNCATED AT 250 WORDS)

Record Date Created: 19900621

Record Date Completed: 19900621

**35/7/4 (Item 4 from file: 155)**

DIALOG(R)File 155:MEDLINE(R)



09083384 PMID: 1788157

**Iontophoretic delivery of a series of tripeptides across the skin in vitro.**

Green P G; Hinz R S; Kim A; Szoka F C; Guy R H

Department of Pharmacy, University of California, San Francisco 94143-0446.

Pharmaceutical research (UNITED STATES) Sep 1991, 8 (9) p1121-7, ISSN 0724-8741--Print Journal Code: 8406521

Contract/Grant No.: HD-27839; HD; NICHD

Publishing Model Print

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

The **iontophoresis** of eight tripeptides, of the general structure alanine-X-alanine, has been measured across hairless mouse **skin** in vitro. The peptides were blocked (a) at the carboxyl terminus using the mixed anhydride reaction with t-butylamine and (b) at the amino terminus by acetylation with 14C-acetic anhydride. The nature of the central residue (X) was varied by selecting one of five neutral amino **acids** , two negatively chargeable moieties (aspartic and glutamic **acids** ), and a positively chargeable species (histidine). **Constant current iontophoresis at 0.36 mA/cm2, using Ag/AgCl electrodes, was performed for 24 hr** in diffusion cells, which allowed both anode and cathode to be situated on the

same (epidermal) side of a single piece of **skin** . Due to a combination of osmotic and electroosmotic forces, the anodal **iontophoretic** flux of neutral peptides was significantly greater than passive transport. Steady-state fluxes were not achieved, however, suggesting that time-dependent **changes** in the properties of the **skin barrier** may be occurring. Limited, further experiments confirmed that, on a 24- **hr** time scale, these **changes** were not fully reversible. The cathodal delivery of anionic permeants was well controlled at a steady and highly **enhanced** rate by the **current** flow. This behavior closely paralleled earlier work using simple negatively charged amino **acids** and N-acetylated amino **acid** derivatives. It appears that the normalized **iontophoretic** flux of these anionic species is independent of lipophilicity but may be inversely related to molecular weight. The positively charged peptide, **Ac** -Ala-His-Ala-NH(But), showed greater anodal **iontophoretic enhancement** when delivered from a donor solution at pH 4.0 than from a solution at pH 7.4.(ABSTRACT TRUNCATED AT 250 WORDS)

Record Date Created: 19920320
Record Date Completed: 19920320

**35/7/14 (Item 14 from file: 73)**

DIALOG(R)File 73:EMBASE

06788825 EMBASE No: 1997070327

**Effect of various physical/chemical properties on the transdermal delivery of cyclosporin through topical application**

Wang D.-P.; Lin C.-Y.; Chu D.-L.; Chang L.-C.
D.-P. Wang, School of Pharmacy, National Defense Medical Center, Taipei Taiwan

Drug Development and Industrial Pharmacy ( DRUG DEV. IND. PHARM. ) ( United States) 1997, 23/1 (99-106)
CODEN: DDIPD ISSN: 0363-9045
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 7

The purpose of this study was to evaluate the effect of (A) **skin** stripping (B) **transdermal enhancer** and (C) **iontophoresis** , on the in vitro **transdermal** delivery of cyclosporin. An in vitro **transdermal** study **through** hairless mouse **skin** using a selected cyclosporin topical formulation was also conducted. Results show that the **permeation** coefficient of cyclosporin was increased as the **skins** were stripped more times. Among the **transdermal enhancers**, azone, salicyclic **acid** , dimethyl **sulfoxide** , sodium lauryl **sulfate** and Tween 20; azone, and dimethyl **sulfoxide** were found to significantly increase the cyclosporin delivery, while salicylic **acid** , sodium lauryl**sulfate** and Tween 20 had no apparent effects. In further studies to define the optimum concentration of the above **enhancers**, the greatest effect was determined to be 1% for azone and 5% for dimethyl **sulfoxide** . Constant **voltage iontophoresis** was proven to be effective in **enhancing** the cyclosporin **transdermal** delivery. **Data show that an increase in the permeability was observed when the voltage was increased from 1 to 7 V** . The results of in vivo topical application of a selected cyclosporin formulation to hairless mouse **skin** indicate that both blood and **skin** concentration reached maximum at about 36 **hr** after application, and that the cyclosporin concentration in the **skin** was constantly higher (10 times at the peak maximum) than its corresponding blood concentration at the same time intervals.

**35/7/15 (Item 15 from file: 34)**
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

06141869 Genuine Article#: XX711 Number of References: 9
**Title: Iontophoretic transdermal absorption of insulin and calcitonin in rats with newly-devised switching technique and addition of urea**
Author(s): Tomohira Y; Machida Y (REPRINT) ; Onishi H; Nagai T
Corporate Source: HOSHI UNIV,DEPT CLIN PHARM, SHINAGAWA KU, EBARA 2-4-41/TOKYO 142//JAPAN/ (REPRINT); HOSHI UNIV,DEPT CLIN PHARM, SHINAGAWA KU/TOKYO 142//JAPAN/; HOSHI UNIV,DEPT PHARMACEUT, SHINAGAWA KU/TOKYO 142//JAPAN/
Journal: INTERNATIONAL JOURNAL OF PHARMACEUTICS, 1997, V155, N2 (SEP 26), P 231-239
ISSN: 0378-5173 Publication date: 19970926
Publisher: ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS
Language: English Document Type: ARTICLE
Abstract: The effect of **urea** and reversing polarity of electrodes (switching technique) in **iontophoresis** was investigated in order to get a better **transdermal** absorption of peptide drugs: insulin and calcitonin, and to reduce dermal irritation caused by the **iontophoresis** . Two cells with an electrode were set on the hair-removed abdominal **skin** of diabetic or oophorectomized rats. After putting peptide solution into the anode side or both of the cells, an electric **current** with pulsed rectangular wave form (4 kHz, 50% duty) was passed through the **skin** for **2 h** at 0.075 mh cm(-2) (insulin) and for **50 min or 2 h** at 0.015 mA cm(-2) (calcitonin). Absorption of insulin and calcitonin was estimated from the reduction of glucose and calcium levels in the plasma of the rats, respectively. When the polarity of electrodes was reversed at intervals of 20 **min** for insulin and 25 **min** for calcitonin, absorption of the drug was effectively **enhanced**. The addition of **urea** to the insulin solution together with the switching technique brought about a remarkably facilitated absorption of insulin. Moreover, comparison of the **skin** conditions between switching and non-switching experiments suggested that irritation of **skin** could be reduced by employment of the switching **iontophoresis** . (C) 1997 Elsevier Science B. **V.**

**35/7/16 (Item 16 from file: 34)**
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

05783891 Genuine Article#: WX067 Number of References: 31
**Title: Acute effects of iontophoresis on human skin in vivo: Cutaneous blood flow and transepidermal water loss measurements**
Author(s): Brand RM; Singh P; AspeCarranza E; Maibach HI; Guy RH
Corporate Source: UNIV CALIF SAN FRANCISCO,DEPT BIOPHARMACEUT SCI, SCH PHARM/SAN FRANCISCO//CA/94143; UNIV CALIF SAN FRANCISCO,DEPT PHARMACEUT CHEM, SCH PHARM/SAN FRANCISCO//CA/94143; UNIV CALIF SAN FRANCISCO,SCH MED, DEPT DERMATOL/SAN FRANCISCO//CA/94143
Journal: EUROPEAN JOURNAL OF PHARMACEUTICS AND BIOPHARMACEUTICS, 1997, V43 , N2 (APR), P133-138
ISSN: 0939-6411 Publication date: 19970400
Publisher: MEDPHARM GMBH SCIENTIFIC PUBL, POSTFACH 10 10 61, D-70009 STUTTGART, GERMANY

Language: English Document Type: ARTICLE
Abstract: The objective of this study was to quantify the acute effects of **iontophoretic current** passage on human **skin** in vivo. Specifically, local **skin** blood flow (SBF) and transepidermal water loss (TEWL) have been measured at the sites of electrode application before and subsequent to **iontophoresis** at **current** levels which are generally considered to be 'reasonable'. Infrared spectra were also recorded at the same **skin** sites using the attenuated total reflectance technique (ATR-IR). **The current levels administered were up to 0.5 mA/cm(2) for a maximum of 25 min** . It was found that **current** application for only 5 **min** was sufficient to cause a significant increase in SBF. Longer periods of **current** flow induced greater **changes** in SBF, the elevated level of which persisted for longer times after the termination of **iontophoresis** . Typically, SBF increased more beneath the anode than beneath the cathode, although visually the degree of irritation was sometimes difficult to distinguish. All subjects were able to feel the application of **current**, the majority registering greater discomfort at the anode. Apart from the occlusive effect of the electrode chamber solutions, **iontophoresis** elicited no significant **change** in TEWL relative to the no-**current** controls, Similarly, ATR-IR detected no major **changes** in the spectroscopic profile of the outer **stratum** corneum. Only relatively **min**or **alter**ations in protein conformational distribution were observed. In summary, the acute effects of **iontophoresis** on human **skin** in vivo are quite moderate. The most significant effect is the rather consistent induction of an erythematous response, the persistence of which depends upon the quantity of charge and the absolute level of **current** delivered. (C) 1997 Elsevier Science B. **V.**

**35/7/17 (Item 17 from file: 94)**
DIALOG(R)File 94:JICST-EPlus
(c)2006 Japan Science and Tech Corp(JST). All rts. reserv.
03112892 JICST ACCESSION NUMBER: 97A0426115 FILE SEGMENT: JICST-E
**The present clinical therapy for keloids and hypertrophic scars and experience of iontophoretic therapy with tranilast.**
SHIGEKI SADAYUKI (1); NOBUOKA NORI (1); IKUTA YOSHIKAZU (1); MURAKAMI TERUO (1); TAKANO MIKIHISA (1); YATA NOBORU (1)
(1) Hiroshima Univ., Sch. of Med.
Drug Deliv Syst, 1997, VOL.12,NO.2, PAGE.115-120, FIG.5, TBL.1, REF.16
JOURNAL NUMBER: X0225AAO ISSN NO: 0913-5006 CODEN: DDSYE
UNIVERSAL DECIMAL CLASSIFICATION: 616.5-085
LANGUAGE: Japanese COUNTRY OF PUBLICATION: Japan
DOCUMENT TYPE: Journal
ARTICLE TYPE: Original paper
MEDIA TYPE: Printed Publication
ABSTRACT: Keloids and hypertrophic scars, especially keloids, are clinically intractable scars caused by an abnormal proliferation of fibroblasts and excessive production of collagen. The present clinical therapy for such scars is described briefly, and the feasibility of **iontophoretic** therapy with tranilast was examined in hairless rats and patients with scars. A drug electrode containing 12 mg tranilast, which was dissolved in 1.5 ml of ethanol/water(8:2v/ **v** ) mixture, was placed on the dorsal **skin** surface of anesthetized rats or the affected parts of patients, and connected to the negative pole. An electric **current** was pulsed **through** at one **min** intervals. The in vivo **current** density

was almost comparable between intact **skin** surfaces of healthy volunteers and keloids/hypertrophic scars of patients. Tranilast given **iontophoretically** (2 mA) a period of 30 **min** a week reduced the patients' complaints of pain and itching after only one or two treatments. Thus, the **transdermal iontophoretic** delivery of tranilast may be a useful treatment for keloid and hypertrophic scars, particularly for relieving pain and itching, and is more beneficial than tranilast given orally. Some discussions were also made in the present report. (author abst.)

**35/7/18 (Item 18 from file: 155)**
DIALOG(R)File 155:MEDLINE(R)

11409411 PMID: 9232700

**Treatment of keloid and hypertrophic scars by iontophoretic transdermal delivery of tranilast.**

Shigeki S; Murakami T; Yata N; Ikuta Y
Department of Orthopedic Surgery, Hiroshima University School of Medicine, Japan.

Scandinavian journal of plastic and reconstructive surgery and hand surgery / Nordisk plastikkirurgisk forening and Nordisk klubb for handkirurgi (SWEDEN) Jun 1997, 31 (2) p151-8, ISSN 0284-4311--Print
Journal Code: 8707869
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

The feasibility of **iontophoretic transdermal** delivery of tranilast (N-(3,4-dimethoxycinnamoyl) anthranilic **acid** ) for the treatment of keloid and hypertrophic scars was evaluated in hairless rats and humans. A drug electrode containing tranilast 1.5 ml (8 mg/ml in ethanol/water (8/2, **v** / **v** ) mixture) was placed on the dorsal **skin** surface of anaesthetised rats or the affected parts of patients, and connected to the negative pole; an electric **current** (0.5-4 mA for rats, 2 mA for people) was pulsed through at one **minute** intervals. Tranilast was effectively delivered **transdermally iontophoretically** into the restricted **skin tissues** of hairless rats and the affected parts of four patients with hypertrophic scars with no **skin** damage. In four other patients tranilast given **iontophoretically** for a period of 30 **minutes** a week reduced the patients' complaints of pain and itching after only one or two treatments although there were some variations among patients. These results indicate that the **transdermal iontophoretic** delivery of tranilast is a useful treatment for keloid and hypertrophic scars, particularly for relieving pain and itching, and is more beneficial than tranilast given orally.

Record Date Created: 19970916
Record Date Completed: 19970916

**35/7/22 (Item 22 from file: 155)**
DIALOG(R)File 155:MEDLINE(R)

11962378 PMID: 9794503

**Localization of a FITC-labeled phosphorothioate oligodeoxynucleotide in the skin after topical delivery by iontophoresis and electroporation.**

Regnier V; Preat V
Universite Catholique de Louvain, Unite de Pharmacie Galenique, Brussels, Belgium.
Pharmaceutical research (UNITED STATES) Oct 1998, 15 (10) p1596-602, ISSN 0724-8741--Print Journal Code: 8406521
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
PURPOSE: The aim of this study was to verify the hypothesis that the application of high **voltage** to the **skin** **enhances** both **stratum** corneum and keratinocyte **permeab**ility. Therefore, the transport of FITC labelled phosphorothioate oligonucleotides (FITC-PS) administered by passive diffusion, **iontophoresis** or electroporation was localized. METHODS: Fluorescent microscopy and laser scanning confocal microscopy were used to visualize the FITC-PS transport at the **tissue** and cell level respectively in hairless rat **skin** after electroporation (5 x (200 **V** approximately 500 ms) or **iontophoresis** (same amount of charges transferred). RESULTS: FITC-PS did not penetrate the viable **skin** by passive diffusion. Molecular transport in the **skin** upon electroporation or **iontophoresis** was localized and implied mainly hair follicles for **iontophoresis** . In the **stratum** corneum, the pathways for FITC-PS transport were more transcellular during electroporation and paracellular during **iontophoresis** . FITC-PS were detected in the nucleus of the keratinocytes a few **minutes** after pulsing. In contrast, **iontophoresis** did not lead to an uptake of the oligomer. CONCLUSIONS: The internalization of FITC-PS in the keratinocytes after electroporation confirms the hypothesis and suggests that electroporation, which allows both efficient topical delivery and rapid cellular uptake of the oligonucleotides, might be useful for antisense therapy of epidermal diseases.
Record Date Created: 19981224
Record Date Completed: 19981224

**35/7/24 (Item 24 from file: 73)**
DIALOG(R)File 73:EMBASE
(c) 2006 Elsevier Science B.V. All rts. reserv.
07711757 EMBASE No: 1999195329
**Transdermally delivered peroxovanadium can lower blood glucose levels in diabetic rats**
Brand R.M.; Hamel F.G.
R.M. Brand, Dept. Biological Systems Eng., 207 L.W. Chase Hall, University of Nebraska, Lincoln, NE 68583-0726 United States
AUTHOR EMAIL: rbrand1@unl.edu
International Journal of Pharmaceutics ( INT. J. PHARM. ) (Netherlands) 1999, 183/2 (117-123)
CODEN: IJPHD ISSN: 0378-5173
PUBLISHER ITEM IDENTIFIER: S037851739900071X
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 33
The element vanadium can have insulin mimetic properties and therefore has been suggested as a possible therapeutic **agent** for treatment of diabetes. A series of peroxovanadium compounds that are more potent at lowering blood glucose levels than sodium metavanadate, sodium

orthovanadate and vanadyl **sulfate** have recently been synthesized. These compounds probably will not be orally active so **transdermal** administration is a potential option. A patch containing either the peroxovanadium compound [VO(Oinf 2)inf 2 1-10 phenanthroline], abbreviated bpV(phen), or placebo was placed on the back of streptozotocin induced diabetic rats and was delivered either passively (16 h) or **iontophoretically** (0.5 mA/cmsup 2 for **4 h**). Blood samples were analyzed for glucose and vanadium levels. Mean blood glucose levels were 83+/-1% and 109+/-1% of the starting values for animals **iontophoretically** treated with bpV(phen) and vehicle, respectively. The compound's insulin mimetic properties were evident within 60 **min** of **current** initiation. Blood glucose levels were reduced to 74+/-14% of the original level after 16 h of passive treatment. The compound was ineffective when fed to animals. **Transdermal** delivery of bpV(phen) resulted in significantly greater blood levels of vanadium than the orally delivered compound (P<0.05). Overall these experiments demonstrate that peroxovanadium delivered through the **skin** can lower blood glucose levels in rats. Further experiments are warranted to better characterize the nature of the response and to determine the potential for using these compounds in humans. Copyright (C) 1999 Elsevier Science B. V.

**35/7/25 (Item 25 from file: 73)**
DIALOG(R)File 73:EMBASE

07710594 EMBASE No: 1999193651
**Transdermal iontophoretic delivery of enoxacin from various liposome-encapsulated formulations**
Fang J.-Y.; Sung K.C.; Lin H.-H.; Fang C.-L.
J.Y. Fang, Graduate Inst. Pharmaceutical Sci., Taipei Medical College, 250 Wu-Hsing Street, Taipei Taiwan
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Journal of Controlled Release ( J. CONTROL. RELEASE ) (Netherlands) 1999, 60/1 (1-10)
CODEN: JCREE ISSN: 0168-3659
PUBLISHER ITEM IDENTIFIER: S0168365999000553
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 32
The major purpose of this work was to study the effect of various liposome formulations on the **iontophoretic** transport of enoxacin through excised rat **skin** . The electrochemical stability of these liposomes was also evaluated. The encapsulation **percentage** of enoxacin was significantly **enhanced after 6 h incubation in an electric field**; whereas the fusion of liposomes was inhibited by application of electric **current**. The results of **iontophoretic** drug transport showed that the **permeab**ility of enoxacin released from liposomes was higher compared with that of free drug. The **iontophoretic permeab**ility of enoxacin released from liposomes increased with a decrease in the **fatty acid** chain length of the phospholipid, which may be due to the different phase transition temperatures of the phospholipids. Incorporation of charged phospholipid resulted in an **alter**ation of the **transdermal** behavior of enoxacin: the **iontophoretic permeat**ion as well as the amount of enoxacin partitioned in **skin** was greatly reduced after incorporation of stearylamine in liposomes, which can be attributed to the competitive ion effect. The enoxacin released from **stratum** corneum-based liposomes showed the highest amount of

enoxacin partitioned into **skin** depot. The results of employing cathodal **iontophoresis** on negative charged liposomes suggested that the liposomal vesicles or phospholipids may carry enoxacin into deeper **skin** strata via the follicular route. Copyright (C) 1999 Elsevier Science B. **V.**

**35/7/31 (Item 31 from file: 155)**
DIALOG(R)File 155:MEDLINE(R)

12810607 PMID: 10925124

**The electrostability and electrically assisted delivery of an organophosphate pretreatment (physostigmine) across human skin in vitro.**

Rowland C A; Chilcott R P
Department of Biomedical Sciences, CBD Porton Down, Wiltshire SP4 0JQ, Salisbury, UK.

Journal of controlled release - official journal of the Controlled Release Society (NETHERLANDS) Aug 10 2000, 68 (2) p157-66, ISSN 0168-3659--Print Journal Code: 8607908
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

Physostigmine is a tertiary carbamate that is utilised as a pretreatment against organophosphate intoxication. Oral delivery of physostigmine is not practical due to high first pass metabolism and short elimination half life. **Transdermal** administration of physostigmine may circumvent such problems. The aim of this study was to assess the electrostability of physostigmine and the feasibility of electrically assisted **transdermal** drug delivery of physostigmine through isolated human **skin** in vitro. Buffered solutions of physostigmine (free base, salicylate and **sulphate** ) were electrostable under conditions of **iontophoresis** and electroporation as measured by HPLC, although instability of the chloridised silver electrodes was observed. Physostigmine **sulphate** was chosen for further study as it appeared to prevent degradation of the electrodes. Under conditions of **iontophoresis** (0.8 mA cm(-2), **applied for 5- or 2.5- min durations for a maximum period of 45 min over 8 h**), the total quantity of physostigmine **sulphate** that penetrated was 6.5+/-2.3% and 3.9+/-1.7% (pH 5.0 and pH 5.5) of the total applied dose (2 mg). Physostigmine did not penetrate the **skin** when electroporated at a frequency of 0.1 Hz or 10 Hz (100 **V** , 1 ms pulse width, duration 1 s, repetition 5-10 s), but significant amounts were delivered at a frequency of 100 Hz, being 11.3+/-2.9% and 5.8+/-2.5% of the applied dose (pH 5.0 and pH 5.5, respectively). These data indicate that **iontophoretic** and electroporative drug delivery of physostigmine **sulphate** was buffer-dependent, an effect tentatively attributed to a combination of co-ion competition, mono/di-cation ratio and applied charge effects.

Record Date Created: 20000920
Record Date Completed: 20000920

**37/6/1 (Item 1 from file: 5)**
0002615623 BIOSIS NO.: 197967004618

**DIFFERENTIAL EFFECTS OF MORPHINE ON FORE ARM BLOOD FLOW ATTENUATION OF SYMPATHETIC CONTROL OF THE CUTANEOUS CIRCULATION**

1978

**37/6/2 (Item 2 from file: 5)**
0003898812 BIOSIS NO.: 198375082755
**EFFECTS OF INTRA VENOUSLY ADMINISTERED ENANTIOMERS OF BACLOFEN ON FUNCTIONALLY IDENTIFIED UNITS IN LUMBAR DORSAL HORN OF THE SPINAL CAT**
1982

**37/6/3 (Item 3 from file: 73)**
03920150 EMBASE No: 1989089143
**Activity-dependent disinhibition. II. Effects of extracellular potassium, furosemide, and membrane potential on E(Cl)sup - in hippocampal CA3 neurons**
1989

**37/6/4 (Item 4 from file: 155)**
08116202 PMID: 2568409
**The location and function of NMDA receptors in cat and kitten visual cortex.**
Jul 1989

**37/6/5 (Item 5 from file: 73)**
05120403 EMBASE No: 1992260619
**GABA-immunoreactive terminals synapse on primate spinothalamic tract cells**
1992

**37/6/6 (Item 6 from file: 34)**
02318759 Genuine Article#: KT661 Number of References: 25
**Title: L-NAME BLOCKS RESPONSES TO NMDA, SUBSTANCE-P AND NOXIOUS CUTANEOUS STIMULI IN CAT DORSAL HORN** (Abstract Available)

**37/6/7 (Item 7 from file: 73)**
05868517 EMBASE No: 1994275261
**Thyrotropin-releasing hormone enhances excitatory postsynaptic potentials in neocortical neurons of the rat in vitro**
1994

**37/6/8 (Item 8 from file: 73)**
05724780 EMBASE No: 1994128053
**Potentiation of a metabotropic glutamatergic response following NMDA receptor activation in rat hippocampus**
1994

**37/6/10 (Item 10 from file: 34)**
04126349 Genuine Article#: RG460 Number of References: 66
**Title: INTEGRATION IN TRIGEMINAL PREMOTOR INTERNEURONS IN THE CAT .3. INPUT CHARACTERISTICS AND SYNAPTIC ACTIONS OF NEURONS IN SUBNUCLEUS-GAMMA OF THE ORAL NUCLEUS OF THE SPINAL TRIGEMINAL TRACT WITH A PROJECTION TO THE MASSETERIC MOTONEURON SUBNUCLEUS** (Abstract Available)

**37/6/11 (Item 11 from file: 73)**
06747939 EMBASE No: 1997029415
**Mechanisms for regulating synaptic efficiency in the visual cortex**
1996

**37/6/12 (Item 12 from file: 73)**
06478339 EMBASE No: 1996144555
**Muscarinic receptors mediating depression and long-term potentiation in**

**rat hippocampus**
1996

**37/6/13 (Item 13 from file: 73)**
06815356 EMBASE No: 1997097848
**Activation of muscarinic receptors modulates NMDA receptor-mediated responses in auditory cortex**
1997

**37/6/16 (Item 16 from file: 155)**
11425352 PMID: 9252236
**Stimulus intensity, cell excitation and the N-methyl-D-aspartate receptor component of sensory responses in the rat spinal cord in vivo.**
Sep 1997

**37/6/17 (Item 17 from file: 34)**
06520852 Genuine Article#: YY734 Number of References: 18
**Title: Tissue extraction and high-performance liquid chromatographic determination of ketoprofen enantiomers** (ABSTRACT AVAILABLE)
Publication date: 19980213

**37/6/19 (Item 19 from file: 73)**
10755841 EMBASE No: 2000236647
**In vivo electrical activity of brainstem neurons in fetal rats during asphyxia**
21 JUL 2000

**37/7/9 (Item 9 from file: 34)**
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 2006 Inst for Sci Info. All rts. reserv.
03385474 Genuine Article#: PA985 Number of References: 26
**Title: ALKALI HALIDE-ASSISTED PENETRATION OF NEOSTIGMINE ACROSS EXCISED HUMAN SKIN - A COMBINATION OF STRUCTURED WATER DISRUPTION AND A DONNAN-LIKE EFFECT**
Author(s): MICHAELBARUCH E; SHIRI Y; COHEN S
Corporate Source: TEL AVIV UNIV,SACKLER SCH MED,DEPT PHYSIOL & PHARMACOL/IL-69978 TEL AVIV//ISRAEL/; CHAIM SHEBA MED CTR,DEPT DERMATOL/RAMAT GAN//ISRAEL/
Journal: JOURNAL OF PHARMACEUTICAL SCIENCES, 1994, V83, N8 (AUG), P 1071-1076
ISSN: 0022-3549
Language: ENGLISH Document Type: ARTICLE
Abstract: The penetration of neostigmine across excised human **skin** mounted in flow-through diffusion cells, delivered from a 0.28 M aqueous solution, was below detection limits. The presence of either NaCl or LiCl in the donor solution caused significant fluxes of neostigmine, with **permeab**ility coefficients (K-p's) in the range of 10(-6) cm **min** (-1). Paradoxically, low concentrations of NaCl or LiCl (0.25 and 0.5 M) were more effective in this respect than the 1 M solution, which was the least effective concentration in the range of 0.25-3 M. Thus, the dependence of the experimental K-p values on inorganic ion concentration followed a biphasic course, suggesting the participation of two distinctive mechanisms in the penetration-**enhanc**ement process. The early phase corresponding to 0.25 and 0.5 M NaCl or LiCl is being partly ascribed to a decrease in the

viscosity of lamellar water caused by the influx of the respective hydrated ions, hydration of LiCl or NaCl being more extensive at low alkali halide concentration that at higher ones (reference cited). The late phase corresponding to 2 and 3 M LiCl and NaCl is partly ascribed to a Donnan-like effect whereby the presence of a large excess of poorly diffusible common ion (Na+ or Li+) **enhance**s the partitioning into the **skin** of the more diffusible ion, in this case neostigmine cation. The presence of inorganic ions at different concentrations had no effect on the partial molar volume of neostigmine bromide ( **V** -I(infinity) = 223.5 cm(3) mol(-1)), which was practically the same for all concentrations of either LiCl and NaCl. **Enhance**ment of the penetration of neostigmine probably by a Donnan-like effect was far more prominent in the presence of benzalkonium cation, which is less likely to penetrate the **skin barrier** in comparison to Li+ or Na+. The K-p's observed were of the order of 10(-5) cm **min** (-1) and showed a clear dependence on benzalkonium chloride molarity in the range of 0.25 to 1 M.

**37/7/15 (Item 15 from file: 155)**
DIALOG(R)File 155:MEDLINE(R)

11649696 PMID: 15989590
**Drug delivery across the skin.**
Cevc G
Medizinische Biophysik, Klinikum r.d.I., Technische Universitat Munchen, Ismaninger Str. 22, D-81675 Munchen, Germany.
Expert opinion on investigational drugs (England) Dec 1997, 6 (12) p1887-937, ISSN 1744-7658--Electronic Journal Code: 9434197
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: PubMed not MEDLINE

Since the introduction of the first through the **skin** (TTS) therapeutic in 1980, a total of 34 TTS products have been marketed and numerous drugs have been tested by more than 50 commercial organisations for their suitability for TTS delivery. Most of the **agents** which have been tested have had low molecular weights, due to the im**permeab**ility of the **skin barrier**. This **barrier** resides in the outermost **skin** layer, the **stratum** corneum. It is mechanical, anatomical, as well as chemical in nature; laterally overlapping cell multi-layers are sealed by tightly packed, intercellular, lipid multi-lamellae. Chemical **skin permeation enhancers** increase the transport across the **barrier** by partly solubilising or extracting the **skin** lipids and by creating hydrophobic pores. This is often irritating and not always well-tolerated. The TTS approach allows drugs (< 400 kDa in size) to **permeate** through the resulting pores in the **skin** , with a short lag-time and subsequent steady-state period. Drug bioavailability for TTS delivery is typically below 50%, avoiding the first pass effect. Wider, hydrophilic channels can be generated by **skin** poration, with the aid of a small electrical **current** (> 0.4 mA/cm2) across the **skin** ( **iontophoresis** ) or therapeutic ultrasound (few W/cm2; sonoporation). High- **voltage** (> 150 **V** , electroporation) widens the pores even more and often irreversibly. These standard poration methods require experience and equipment and are therefore, not practical; at best, charged/small molecules (< or = 4000 kDa in size) can be delivered

efficiently across the **skin** . In spite of the potential harm of gadget-driven **skin** poration, this method is used to deliver molecules which conventional TTS patches are unable to deliver, especially polypeptides. Lipid-based drug carriers (liposomes, niosomes, nanoparticle microemulsions, etc.) were proposed as alternative, low-risk delivery vehicles. Such suspensions provide an improved drug reservoir on the **skin**, but the aggregates remain confined to the surface. Conventional carrier suspensions increase **skin** hydration and/or behave as **skin permeation enhancers** . The recently developed carriers; Transferomes, comprise pharmaceutically-acceptable, established compounds and are thought to penetrate the **skin barrier** along the naturally occurring trans**cutaneous** moisture gradient. Transfersomes are believed to penetrate the hydrophilic (virtual) channels in the **skin** and widen the former after non-occlusive administration. Both small and large hydrophobic and hydrophilic molecules are deliverable across the **stratum** after conjugation with Transfersomes. Drug distribution after **transdermal** delivery probably proceeds via the lymph. This results in quasi-zero order kinetics with significant systemic drug levels reached after a lag-time of up to a few **hours** . The relative efficiency of TTS drug delivery with Transfersomes is typically above 50 %; with the added possibility of regional drug targeting.
Record Date Created: 20050701
Record Date Completed: 20050712

**37/7/18 (Item 18 from file: 34)**
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

08180408 Genuine Article#: 254YL Number of References: 32
**Title: In vitro percutaneous absorption enhancement of propranolol hydrochloride through** porcine epidermis by **terpenes /ethanol**
Author(s): Zhao KD; Singh J (REPRINT)
Corporate Source: N DAKOTA STATE UNIV,COLL PHARM, DEPT PHARMACEUT SCI/FARGO//ND/58105 (REPRINT); N DAKOTA STATE UNIV,COLL PHARM, DEPT PHARMACEUT SCI/FARGO//ND/58105
Journal: JOURNAL OF CONTROLLED RELEASE, 1999, V62, N3 (DEC 6), P359-366
ISSN: 0168-3659 Publication date: 19991206
Publisher: ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS
Language: English Document Type: ARTICLE
Abstract: The purpose of this study was to investigate the mechanism(s) of per**cutaneous** absorption **enhance**ment of propranolol hydrochloride (PHCL) across porcine epidermis by **terpenes** (e.g. menthone and limonene) in combination with ethanol. The in vitro per**cutaneous** absorption experiments were performed using Franz diffusion cells. The solubility of PHCL in control and **enhance**r solutions was determined **th**rough high-performance liquid **ch**romatography. Partitioning of PHCL to powdered SC from control or **enhance**r solutions was also determined in order to investigate the binding of PHCL to the SC from the SC/**enhance**r system. Fourier transform infrared spectroscopy (FT-LR) was employed to study the biophysical **changes** in **stratum** corneum (SC) lipids. The in vitro macroscopic **barrier** properties were investigated by measuring transepidermal water loss (TEWL) using Tewameter(TM). Five **percent** menthone or limonene in combination with ethanol (EtOH) (menthone/EtOH or limonene/EtOH) significantly increased ($P<0.05$) the flux of PHCL **th**rough porcine epidermis in comparison to the control (EtOH). The partitioning of PHCL to the SC from the SC/**enhance**r system was also significantly greater than the SC/control system. The above **enhance**rs

showed a decrease in the peak heights and areas for both asymmetric and symmetric C-H stretching absorbances in comparison with the untreated SC, indicating the SC lipids extraction. Menthone/EtOH and limonene/EtOH **enhanced** (P<0.05) the in vitro TEWL **through** the epidermis in comparison to the control. Thus, an **enhancement** in the flux of PHCL, by menthone/EtOH and limonene/EtOH is due to SC lipid extraction, macroscopic **barrier** perturbation, and improvement in the partitioning of the drug to the SC. 

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File 377:Derwent Drug File 1983-2006/Jun W1
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File 376:Derwent Drug File 1964-1982
         (c) 1995 Thomson Derwent
File  74:Int.Pharm.Abs 1970-2006/May B2
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File   2:INSPEC 1898-2006/Jun W4
         (c) 2006 Institution of Electrical Engineers
File 164:Allied & Complementary Medicine 1984-2006/Jul
          (c) 2006 BLHCIS
Set     Items   Description
S1       4351   IONTOPHORE? OR MICROIONTOPHORE?
S2     542850   TISSUE OR SKIN OR MUCOSA? ? OR CUTANEOUS? OR TRANSDERMAL?
S3    1884272   V OR VOLT OR VOLTS OR VOLTAGE? ?
S4     294569   PERCENT??? OR PER()CENT???
S5     171009   ac OR ALTERNATING()CURRENT
S6     554873   min OR mins OR minUTE? ? OR hr OR HOUR OR HOURS OR HRS
S7     388932   BARRIER? ? OR STRATUM OR PERMEAT? OR PERMEAB?
S8    2048495   AGENT? ? OR ENHANCE? OR ENHANCING OR MODIFY??? OR MODIFIE?
            ? OR MODIFICATION
S9    2058436   CHANGE? ? OR CHANGING OR ALTER????
S10     81045   FATTY()(ACID? ? OR ALCOHOL? ?) OR BILE()(ACID? ? OR SALT? -
            ?) OR (NONIONIC OR ANIONIC OR CATIONIC OR AMPHOTERIC)()SURFAC-
            TANT? ?
S11    347175   (ORGANIC OR HYDROCARBON)(1W)SOLVENT? ? OR ESTER? ? OR AMID-
            E? ? OR PYRROLIDONE? ? OR CYCLODEXTRIN? ?
S12    157803   SULFOXIDE? ? OR SULPHOXIDE? ? OR SULFATE? ? OR SULPHATE? ?
            OR SULFONATE? ? OR SULPHONATE? ?
S13   1058882   AZACYCLOALK?NONE? ? OR UREA OR TERPENE? ? OR ACID? ? OR AL-
            COHOL? ? OR DIOL? ? OR POLYOL? ?
S14     28657   FATTY()ETHER? ? OR LACTATE? ? OR MYRISTYL? ? OR PALMITATE?
            ? OR LINOLEATE? ?
S15        53   S1 AND S2 AND (S3 OR S5) AND (S4 OR S6)
S16        29   (S7 OR S10:S14) AND S15
S17        25   RD  (unique items)
S18         4   S17/2002
S19         4   S17/2003
S20         2   S17/2004
S21         3   S17/2005
S22         0   S17/2006
S23         0   S17/2001
S24        12   S17 NOT S18:S21
S25        12   Sort S24/ALL/PY,A

25/6/3     (Item 3 from file: 285)
00682348
Effect of electroporation on  transdermal  iontophoretic  delivery of
  luteinizing hormone releasing hormone (LHRH) in vitro.
```

**25/6/5 (Item 5 from file: 377)**
00585817 DERWENT ACCESSION NUMBER: 94-19950
**Comparison between the iontophoretic and passive transdermal delivery of timolol maleate across human cadaver skin.** , 1994

**25/6/6 (Item 6 from file: 377)**
00582684 DERWENT ACCESSION NUMBER: 94-16756
**Integrative Cardiovascular Actions of a Novel Catecholamine, GP-2-128.**, 1994

**25/6/8 (Item 8 from file: 285)**
00864943
**Transdermal iontophoretic delivery of insulin using a photoetched microdevice**

**25/6/10 (Item 10 from file: 285)**
00971885
**Transdermal delivery of cyclosporin-A using electroporation.**

**25/6/11 (Item 11 from file: 8)**
05234511
**Title: In vivo efficacy and safety of skin electroporation**
Publication Year: 1999

**25/6/12 (Item 12 from file: 377)**
00885544 DERWENT ACCESSION NUMBER: 2000-24471
**The effect of electroporation on ionotophoretic transdermal delivery of calcium regulating hormones.**, 2000

**25/7/1 (Item 1 from file: 377)**
DIALOG(R)File 377:Derwent Drug File
(c) 2006 The Thomson Corp. All rts. reserv.
00308886 DERWENT ACCESSION NUMBER: 89-01837
**Skin Electrical Properties and Transdermal Iontophoretic Delivery of Arginine Vasopressin (AVP).**
Lelawongs P; Liu J C; Chien Y W
Pharmacologist 30, No. 3, A27, 1988
ABSTRACT:
This study correlated the electrical properties of excised hairless rat **skin** during a prolonged passage of pulse **current** with the **iontophoretic skin permeation** of arginine vasopressin (AVP). **Current- voltage** relationship had a nonlinear behavior when the applied **current** exceeded a certain value. At this region, the **skin** impedance decreased rapidly during the first 10- **min** application, and then approached plateau. The decrease may be responsible for the **enhanced** AVP flux. Removal of the **stratum** corneum reduced the **skin** impedance and no **enhancement** in the transport of AVP was observed. (congress abstract).

**25/7/2 (Item 2 from file: 377)**
DIALOG(R)File 377:Derwent Drug File
(c) 2006 The Thomson Corp. All rts. reserv.
00569897 DERWENT ACCESSION NUMBER: 94-03754
**The Use of Dermal Clearance Enhancers to Improve the Transdermal Iontophoretic Delivery of Arbutamine.**

Studebaker T L; Hillman R S
Gensia (San Diego, California, United States)
Pharm.Res. 10, No. 10, Suppl., S226, 1993
ABSTRACT:
**Transdermal iontophoretic** (TDI) delivery of arbutamine (AR) is a potential **alternative** to i. **v** . delivery. TDI delivery of AR is limited by dermal build-up of drug which may prolong the offset time. The effect of pretreatment of the **skin** site with dermal clearance **enhancers** (DCE), including chemical counter irritants and vasodilators, on clearance was investigated in the conscious dog. The offset of **hr** after AR **iontophoresis** was reduced with DCE pretreatment vs. untreated control. In 4 normal volunteers who had topical application of DCE to the arm, formulations containing both chemical counter irritants and vasodilators in an **alcohol** -based vehicle were the most effective in increasing blood flow. The marked increase in blood flow may explain increased dermal clearance. (congress abstract).

**25/7/7 (Item 7 from file: 285)**
DIALOG(R)File 285:BioBusiness(R)
(c) 2006 The Thomson Corporation. All rts. reserv.
00904924
**Macromolecules as novel transdermal transport enhancers for skin electroporation.**
Vanbever R; Prausnitz M R; Preat V
Unite de Pharmacie galenique, Ecole de Pharmacie, Univ. Catholique de Louvain, Brussels, Belgium.
Pharmaceutical Research (New York) Vol.14, No.5, p.638-644, 1997.
ABSTRACT: Purpose: Macromolecules were investigated as chemical **enhancers** of **transdermal** transport by **skin** electroporation. Although unable to **enhance** passive or **iontophoretic** transport, macromolecules are proposed to **enhance** electroporation-assisted delivery by stabilizing the increased **permeability** caused by high- **voltage** pulses. Methods: To test this hypothesis, we examined the timescale of transport, the influence of electrical protocol and the influence of macromolecule size, structure, and charge on **enhancement** of **transdermal** mannitol transport in vitro by heparin, dextran- **sulfate** , neutral dextran, and poly-lysine. Results: **Skin** electroporation increased **transdermal** mannitol delivery by approximately two orders of magnitude. The addition of macromolecules further increased transport up to five-fold, in support of the proposed hypothesis. Macromolecules present during pulsing **enhanced** mannitol transport after pulsing for **hours** , apparently by a macromolecule- **skin** interaction. No **enhancement** was observed during passive diffusion or low-**voltage** **iontophoresis** , suggesting that macromolecules interact specifically with transport pathways created at high **voltage** . Although all macromolecules studied **enhanced** transport, those with greater charge and size were more effective. Conclusions. This study demonstrates that macromolecules can be used as **transdermal** transport **enhancers** uniquely suited to **skin** electroporation.

**25/7/9 (Item 9 from file: 377)**
DIALOG(R)File 377:Derwent Drug File
(c) 2006 The Thomson Corp. All rts. reserv.
00761899 DERWENT ACCESSION NUMBER: 97-40404
**Electrically enhanced transdermal delivery of domperidone.**

Jadoul A; Preat V
Univ.Catholique-Louvain (Brussels, Belg.)
Int.J.Pharm. 154, No. 2, 229-34, 1997
ABSTRACT:
**Transdermal** domperidone (Janssen) **permeation** was **enhanced** by **iontophoresis** in hairless rat **skin** in-vitro. Application of high **voltage** pulses markedly increased domperidone **permeation** vs. passive diffusion and **iontophoresis** . Domperidone **permeation** remained elevated for several **hr** after pulsing. Application of a high **voltage** pulse plus **iontophoresis** had synergistic effects on domperidone **permeation** . Domperidone delivery was not **enhanced** by **iontophoresis** or electroporation compared with the use of chemical **enhancers**, but the advantages of electrically **enhanced** delivery, i.e. rapidity and control of the dose delivered, suggest its potential usefulness.

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File 373:Adis Clinical Trials Insight 1982-June 2000
         (c) 2003 ADI BV
File 149:TGG Health&Wellness DB(SM) 1976-2006/Jun W3
         (c) 2006 The Gale Group
File   9:Business & Industry(R) Jul/1994-2006/Jul 06
         (c) 2006  The Gale Group
File  16:Gale Group PROMT(R) 1990-2006/Jul 06
         (c) 2006 The Gale Group
File 160:Gale Group PROMT(R) 1972-1989
         (c) 1999 The Gale Group
File 135:NewsRx Weekly Reports 1995-2006/Jul W1
         (c) 2006 NewsRx
File 148:Gale Group Trade & Industry DB 1976-2006/Jul 04
         (c)2006 The Gale Group
File 129:PHIND(Archival) 1980-2006/Jun W4
         (c) 2006 Informa UK Ltd
File 107:Adis R&D Insight 1986-2006/Jun W2
         (c) 2006 Adis Data Information BV.
File 636:Gale Group Newsletter DB(TM) 1987-2006/Jul 06
         (c) 2006 The Gale Group
File 621:Gale Group New Prod.Annou.(R) 1985-2006/Jul 05
         (c) 2006 The Gale Group
File 173:Adis Clinical Trials Insight 2000-2006/Jun W4
         (c) 2006 ADI BV.
File 429:Adis Newsletters(Archive) 1982-2006/Jul 07
         (c) 2006 ADI BV.
File 441:ESPICOM Pharm&Med DEVICE NEWS 2006/Jan W4
         (c) 2006 ESPICOM Bus.Intell.
Set     Items   Description
S1       1786   IONTOPHORE? OR MICROIONTOPHORE?
S2     741131   TISSUE OR SKIN OR MUCOSA? ? OR CUTANEOUS? OR TRANSDERMAL?
S3    1322943   V OR VOLT OR VOLTS OR VOLTAGE? ?
S4    5518380   PERCENT??? OR PER()CENT???
S5     168670   ac OR ALTERNATING()CURRENT
S6    3411010   min OR mins OR minUTE? ? OR hr OR HOUR OR HOURS OR HRS
S7     500534   BARRIER? ? OR STRATUM OR PERMEAT? OR PERMEAB?
S8    4885056   AGENT? ? OR ENHANCE? OR ENHANCING OR MODIFY??? OR MODIFIE?
            ? OR MODIFICATION
S9      53401   FATTY()(ACID? ? OR ALCOHOL? ?) OR BILE()(ACID? ? OR SALT? -
            ?) OR (NONIONIC OR ANIONIC OR CATIONIC OR AMPHOTERIC)()SURFAC-
            TANT? ?
S10     56488   (ORGANIC OR HYDROCARBON)(1W)SOLVENT? ? OR ESTER? ? OR AMID-
            E? ? OR PYRROLIDONE? ? OR CYCLODEXTRIN? ?
S11     57240   SULFOXIDE? ? OR SULPHOXIDE? ? OR SULFATE? ? OR SULPHATE? ?
            OR SULFONATE? ? OR SULPHONATE? ?
S12    721583   AZACYCLOALK?NONE? ? OR UREA OR TERPENE? ? OR ACID? ? OR AL-
            COHOL? ? OR DIOL? ? OR POLYOL? ?
S13     12866   FATTY()ETHER? ? OR LACTATE? ? OR MYRISTYL? ? OR PALMITATE?
            ? OR LINOLEATE? ?
S14        45   S1(S)S2(S)S3
S15         0   S1(S)S2(S)S5(S)S6
S16        24   S14(S)S7:S13
S17        19   RD  (unique items)
S18         0   S17/2002
S19         1   S17/2003
S20         0   S17/2004
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S21 7 S17/2005
S22 7 S17/2005
S23 0 S17/2006
S24 11 S17 NOT S19:S22
**S25 11 Sort S24/ALL/PD,A**

**25/6/3 (Item 3 from file: 148)**
DIALOG(R)File 148:(c)2006 The Gale Group. All rts. reserv.
06087444 SUPPLIER NUMBER: 12406416 (USE FORMAT 7 OR 9 FOR FULL TEXT)
**MASSACHUSETTS INSTITUTE OF TECHNOLOGY AND CYGNUS ANNOUNCE RESEARCH MILESTONE ON ELECTROPORATION**
July 30, 1992
WORD COUNT: 787 LINE COUNT: 00067

**25/3,K/1 (Item 1 from file: 149)**
DIALOG(R)File 149:TGG Health&Wellness DB(SM)
(c) 2006 The Gale Group. All rts. reserv.
01300534 SUPPLIER NUMBER: 10904399 (USE FORMAT 7 OR 9 FOR FULL TEXT)
**Iontophoresis. (technique used to deliver compounds across the skin under the influence of an electrical current)**
Sarpotdar, Pramod P.
Cosmetics and Toiletries, v106, n6, p94(7)
June, 1991
PUBLICATION FORMAT: Magazine/Journal ISSN: 0361-4387 LANGUAGE: English
RECORD TYPE: Fulltext TARGET AUDIENCE: Trade
WORD COUNT: 3878 LINE COUNT: 00356
... appear to be platinum, carbon or silver/silver chloride. Transport of a cationic compound is **enhanced** by inserting the anode in the formulation and the cathode in the receptor. This configuration...
...the surface area of the electrode does not appear to be a major factor during **iontophoresis** , there are several other complications one must be aware of. The electrolysis of water at the applied **voltage** results in the formation of gas, which gets trapped beneath the **skin** in an in vitro setup. This problem appears to be more acute with platinum electrodes...
...is to use cells with side-by-side geometry, thus preventing bubbles from contacting the **skin** .
2. pH: In addition to bubble formation, the electrolysis of water also causes a significant...J Am **ac** Dermatol, 16(4) 828(1987) [2]ML Elgart and G Fuchs, Tapwater **iontophoresis** in the treatment of hyperhydrosis, Pharmacol and Ther, 26(3) 194 (1987) [3]I Davidson...
...anesthesia, JADA, 88, 125(1974) [5]LP Gangarosa and AL Buettner, Four month results with **iontophoretic** tooth desensitization, J Dental Res, 66, 151 (1987) [6]JM Glass, RL Stephen and SC Jacobsen, The quantity and distribution of ra**diol**abeled dexamethasone delivered to **tissue** by **iontophoresis** , I J Dermatol, 19(9) 519 (1980) [7]P Tyle, **Iontophoretic** devices for drug delivery, Pharm Res, 3(6) 318 (1986) [8]AK Banga and YW Chien, **Iontophoretic** delivery of drugs: Fundamentals, developments and biomedical applications, J Contr Rel, 7, 1 (1988) [9]JB Sloan and K Soltani, **Iontophoresis** in dermatology, J Am Acad Dermatol, 15(4) 671(1986) [10]AJ Singh and MS Roberts, **Transdermal** delivery of drugs by **iontophoresis** : A review, Drug Des Del, 4, 1 (1989) [11]RL Stephen, TJ Petelenz and SC Jacobsen, Potential novel methods for insulin administration: I. **Iontophoresis** , Biomed Biochim Acta, 43, 553 (1984) [12]B Kari, Control of blood glucose levels in alloxan-diabetic rabbits by

**iontophoresis** of insulin, Diabetes, 35, 217 (1986) [13]YW Chien, O Siddiqui, W-M Shi, P Lelawongs and J-C Liu, Direct **current iontophoretic transdermal** delivery of peptide and protein drugs, J Pharm Sci, 78(5) 376 (1989) [14]GW Cleary, **Transdermal** drug delivery, Cosm & Toil, 106(5) 97-109 (1991) [15]PH Dugard and RJ Scheuplein, Effects of ionic **surfactants** on **permeability** of human epidermis: An electrometric study, J Invest Dermatol, 60, 263 (1973) [16]RR Burnette and D Marrero, Comparison between the **iontophoretic** and passive transport of thyrotropin releasing hormone across excised nude mouse **skin** , J Pharm Sci, 75(8) 738 (1986) [17]RJ Scheuplein and IH Bank, Physiol Rev...
...702 (1971) [18]RR Burnette and B Ongpipattanakul, Characterization of the pore transport properties and **tissue alter**ation of excised human **skin** during **iontophoresis** , J Pharm Sci, 77 132 (1988) [19]RR Burnette and B Ongpipattanakul, Characterization of the permselective properties of excised human **skin** during **iontophoresis** , J Pharm Sci, 76(10) 765 (1987) [20]MJ Pikal and S Shah, Transport of uncharged species by **iontophoresis** : Electrophoretic flow, Pharm Res, 3(5) suppl, 79 (1986) [21]N Harper Bellantone, S Rim, ML Francoeur and B Rasadi, **Enhanced** per**cutaneous** absorption via **iontophoresis** I. Evaluation of an in vitro system and transport of model compounds, I J Pharm, 30, 63 (1986) [22]PP Sarpotdar, CR Daniels, GG Liversidge and LA Stemson, Facilitated **iontophoretic** delivery of thyrotropin releasing hormone (TRH) across cadaver **skin** by optimization of formulation variables, Pharm Res, 6 suppl, 107 (1989) [23]T Masada, **WI HIguchi**, **V** Srinivasan, U Ro**hr**, J Fox C Behland S Pons, Examination of iontophrotic **iontophoretic** transport of ionic drugs across **skin** ; baseline studies with four-electrode system, I J Pharm, 49, 57 (1989) [24]L Wearley, J-C Liu and YW Chien, **Iontophoresis** -facilitated **transdermal** delivery of verapamil. I. in vitro evaluation and mechanistic studies, ...C. Cullander, RS Hinz and RH Guy, A new system for in vitro studies of **iontophoresis** , Pharm Res, 5(7) 443 (1988) [26]JB Phipps and DF Untereker, **Iontophoretic** drug delivery, US Patent 4,747,819, May 31 (1988) [27]TJ Petelenz, RL Stephen and SC Jacobsen, Methods and apparatus for **iontophoresis** application of medicaments, US Patent 4,752,285, Jun 21 (1988) [28]JE Sanderson and SR Deriel, Method and apparatus for **iontophoretic** delivery, US Patent 4,722,726, Feb 2 (1988) [29]PP Sarpotdar and CR Daniels, Use of polymeric buffers to facilitate **iontophoretic** transport of drugs, Pharm Res, 7 suppl, 185 (1990) [30]K Okabe, H Yamaguchi and Y Kawai, New **iontophoretic transdermal** administration of the beta-blocker metoprolol, J Contr Rel, 4, 79 (1966) [31]YW Chien, O Siddiqui, Y Sun, WM Shi and JC Liu, **Transdermal iontophoretic** delivery of therapeutic peptides/proteins I: Insulin, Annals of NY Acad Sci, 507, 32 (1987...

**25/3,K/5 (Item 5 from file: 636)**
DIALOG(R)File 636:Gale Group Newsletter DB(TM)

02502831 Supplier Number: 45029154 (USE FORMAT 7 FOR FULLTEXT)
**Part II of lI The Competitive and Growing Alternative Drug Delivery Market**
The BBI Newsletter, v17, n10, pN/A
Oct, 1994
Language: English Record Type: Fulltext
Document Type: Newsletter; Trade
Word Count: 1482
... polymer-based delivery systems. In fact, numerous companies have **transdermal** nitroglycerin products on the market.

**Transdermal** companies also are investigating the use of electricity to aid in **transdermal** delivery. Passive **transdermal** systems are limited in scope because the **skin** 's outer protective layer, the **stratum** corneum, effectively keeps out most molecules. **Iontophoresis** , an FDA-approved method for **transdermal** drug delivery, uses electric potential (a low **voltage**, long -duration **current**) to **enhance** drug efficiency. CYGNUS THERAPEUTIC SYSTEMS has combined **iontophoresis** with electrophoresis (a high- **voltage** , short-duration **current**) to **enhance** drug entry through the **skin** . Overall, this procedure will provide better control of drug delivery and provide site-specific delivery...

**25/3,K/7 (Item 7 from file: 636)**
DIALOG(R)File 636:Gale Group Newsletter DB(TM)
(c) 2006 The Gale Group. All rts. reserv.
03333233 Supplier Number: 46853681 (USE FORMAT 7 FOR FULLTEXT)
**Alternative systems will play a greater role in biopharmaceutical delivery by the year 2005**
The BBI Newsletter, v19, n11, pN/A
Nov 1, 1996
Language: English Record Type: Fulltext
Document Type: Newsletter; Trade
Word Count: 3430
... Pharmaceuticals (Miami, Florida) and Theratech (Salt Lake City, Utah).

Aside from creating thinner, less-irritating **transdermal** patches, with better control, companies also are investigating the use of electricity to aid in **transdermal** delivery. Passive **transdermal** systems are limited in scope because the **skin** 's outer protective layer, the **stratum** corneum, effectively keeps out most molecules. **Iontophoresis** , an FDA-approved method for **transdermal** drug delivery, uses electric potential (a low- **voltage** , long-duration **current**) to **enhance** drug efficiency. Cygnus has combined **iontophoresis** with electrophoresis (a high **voltage** , short duration **current**) to significantly **enhance** drug entry through the **skin** . The procedure will provide better control of drug delivery, and site-specific delivery in peripheral **tissues**. Elan and Genetronics (San Diego, California) also are developing electrically assisted **transdermal** systems. Their products are in Phase III for delivery of calcitonin and Phase II for...

**25/3,K/10 (Item 10 from file: 9)**
DIALOG(R)File 9:Business & Industry(R)
(c) 2006 The Gale Group. All rts. reserv.
02025337 Supplier Number: 24491871 (USE FORMAT 7 OR 9 FOR FULLTEXT)
**Drug Delivery Systems--Markets and Trends**
**(Worldwide oral drug delivery market is anticipated to reach $15 bil in 2000; trends in drug delivery systems market are outlined)**
Medical & Healthcare Marketplace Guide, p I-485+
1999
DOCUMENT TYPE: Journal (United States)
LANGUAGE: English RECORD TYPE: Fulltext
WORD COUNT: 1655
(USE FORMAT 7 OR 9 FOR FULLTEXT)
TEXT:
...delivery which can be easily terminated by patch or product removal.

The leading company in **transdermal** delivery is ALZA Corporation, with **transdermal** products on the market for pain, smoking cessation, HRT, and hypertension. Aside from creating thinner, less-irritating **transdermal** patches with better control, companies are investigating electrotransport to aid in **transdermal** delivery. Passive **transdermal** systems are limited in scope because the **skin** 's outer protective layer, the **stratum** corneum, effectively keeps out most molecules. **Iontophoresis** , an FDA-approved method for **transdermal** drug delivery, uses an electric potential (a low- **voltage** , long-duration **current**) to **enhance** drug efficiency. Genetronics is developing electrically-assisted **transdermal** systems. Its products are in clinical trials using a novel electroporation technology. Trans**mucosa**l delivery continues...
...administration route of high interest for the delivery of proteins and peptides due to high **permeability** of **mucosal** **tissue** . TheraTech and Eli Lilly have formed an agreement for the oral trans**mucosa**l delivery of undisclosed...

**25/7/4 (Item 4 from file: 16)**
DIALOG(R)File 16:Gale Group PROMT(R)

03039846 Supplier Number: 44132665 (THIS IS THE FULLTEXT)
**Will Transdermal Patches Survive A Nicotine Fit? -- New Technology Currents: Electricity**
Genesis Report-Rx, v2, n6, pN/A
Oct, 1993
TEXT:
Active **transdermal** systems reduce the resistance of the **skin** by forcing ionized drugs through the **skin**'s outermost layer, the **stratum** corneum. One method, **iontophoresis**, utilizes an electrical **current** to drive ionic drugs across **skin**. By applying a **minute** electrical charge against a similarly charged molecule, the drug's molecule is propelled through the **skin** into the underlying **tissue**. This technology is particularly useful for applications requiring either site-specific delivery in high therapeutic concentrations or the continuous or semi-continuous controlled delivery of medications that, because of their molecular size, structure, or potency, cannot be delivered by other noninvasive methods.

However, **iontophoresis** poses certain risks. Low **voltages** can cause burns, and excessive **voltage** can induce cardiac arrest. An **alternative** active technique in development is electroporation, which uses pulsed electrical fields to temporarily **enhance** the **permeability** of cell and **tissue** membranes. When the electrical field is withdrawn, the lipids revert to their original orientation, closing the pathway and reversing the temporary increase in **permeability.**



**25/7/9 (Item 9 from file: 135)**
DIALOG(R)File 135:NewsRx Weekly Reports

0000025400 (THIS IS THE FULLTEXT)
**"Localization of a FITC-Labeled Phosphorothioate Oligodeoxynucleotide in the Skin After Topical Delivery by Iontophoresis and Electroporation."**
Gene Therapy Weekly, November 30, 1998, p.13
DOCUMENT TYPE: Research News LANGUAGE: English

RECORD TYPE: FULLTEXT
AUDIENCE: Professional
WORD COUNT: 276
TEXT: According to the authors' abstract of an article published in Pharmaceutical Research, "Purpose: The aim of this study was to verify the hypothesis that the application of high **voltage** to the **skin** **enhances** both **stratum** corneum and keratinocyte **permeability** . Therefore, the transport of FITC-labeled phosphorothioate oligonucleotides (FITC-PS) administered by passive diffusion, **iontophoresis** , or electroporation was localized. Methods: Fluorescent microscopy and laser scanning confocal microscopy were used to visualize the FITC-PS transport at the **tissue** and cell level respectively in hairless rat **skin** after electroporation (5x(200V similar to 500 ms) or **iontophoresis** (same amount of charges transferred). Results: FITC-PS did not penetrate the viable **skin** by passive diffusion. Molecular transport in the **skin** upon electroporation or **iontophoresis** was localized and implied mainly hair follicles for **iontophoresis** . In the **stratum** corneum, the pathways for FITC-PS transport were more transcellular during electroporation and paracellular during **iontophoresis** . FITC-PS were detected in the nucleus of the keratinocytes a few **min**utes after pulsing. In contrast, **iontophoresis** did not lead to an uptake of the oligomer. Conclusions: The internalization of FITC-PS in the keratinocytes after electroporation confirms the hypothesis and suggests that electroporation, which allows both efficient topical delivery and rapid cellular uptake of the oligonucleotides, might be useful for antisense therapy of epidermal diseases." The corresponding author for this study is: V Preat, Univ Catholique Louvain, Unite Pharm Galen, Ave E Mounier, 73 Ucl 73-20, B-1200 Brussels, Belgium. For subscription information for this journal, contact the publisher: Plenum Publ Corp, 233 Spring St, New York, NY 10013. (Authors) Regnier, V .; Preat, V . (Journal) Pharmaceutical Research, October 1998;15(10):1596-1602.

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FILE 'HCAPLUS' ENTERED AT 11:57:37 ON 07 JUL 2006
L1          5785 S IONTOPHORE?
L2        965908 S TISSUE OR SKIN OR MUCOSA# OR TRANSDERMAL## OR CUTANEOUS##
L3        223525 S PERMEAB?
L4          3431 S (MODIFY? OR MODIFIE# OR ALTER### OR CHANGE? OR CHANGING)(3A)B
L5       1331416 S V OR VOLT OR VOLTS OR VOLTAGE
L6        283669 S PERCENT#### OR PER CENT####
L8        101083 S AC OR ALTERNATING CURRENT#
L9       1937658 S MIN OR MINUTE# OR HR OR HOUR#
L10       404571 S FATTY (W)(ACID# OR ALCOHOL#) OR BILE (W)(ACID# OR SALT#) OR (
L11      1006424 S (HYDROCARBON OR ORGANIC)(W)SOLVENT# OR ESTER# OR AMIDE# OR PY
L12       245469 S N ALKYL AZACYCLOALKANONE# OR N ALKYL AZACYCLOALKENONE# OR URE
L13       777478 S FATTY ETHER# OR LACTATE# OR MYRISTYL# OR PALMITATE# OR LINOLE
L14         1909 S L1 AND L2
L15          273 S (L5 OR L8) AND L14
L16           50 S L15 AND L3
L17            2 S L15 AND L4
L18            6 S L15 AND L10
L19           10 S L15 AND L11
L20            8 S L15 AND L12
L21           15 S L15 AND L13
L22           36 S L17 OR L18 OR L19 OR L20 OR L21
L23            9 S L22 AND (L6 OR L9)
L24           43 S L16 NOT L22
L25           11 S L24 AND (L6 OR L9)
```

**L23 ANSWER 4 OF 9 HCAPLUS COPYRIGHT 2006 ACS on STN**

ACCESSION NUMBER: 1998:780549 HCAPLUS <<LOGINID::20060707>>
DOCUMENT NUMBER: 130:257213
**TITLE:** **In vivo efficacy and safety of ***skin*** electroporation**
AUTHOR(S): Vanbever, Rita; Preat, Veronique
CORPORATE SOURCE: School of Pharmacy, Department of Pharmaceutical Technology, Catholic University of Louvain, Brussels, Belg.
SOURCE: Advanced Drug Delivery Reviews (1999), 35(1), 77-88
CODEN: ADDREP; ISSN: 0169-409X
PUBLISHER: Elsevier Science Ireland Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 51 refs. This article reviews the studies on ***skin*** electroporation carried out in vivo in animals and emphasizes its potential therapeutic applications for ***transdermal*** and topical drug delivery. In agreement with in vitro studies, transport across ***skin*** due to high- ***voltage*** pulses in vivo was shown to increase by orders of magnitude on a timescale of ***minutes*** . Increased ***transdermal*** transport was measured by systemic blood uptake and/or pharmacol. response, and demonstrated for calcein, a fluorescent tracer, fentanyl, a potent analgesic and flurbiprofen, an antiinflammatory drug. Combined electroporation with ***iontophoresis*** was shown to provide rapidly responsive ***transdermal*** transport of LH releasing hormone ex vivo as well. These data underline the potential of ***skin*** electroporation for improving the delivery profile of existing conventional ***transdermal*** patches, but also for replacing the injectable route. High- ***voltage*** pulses can increase drug permeation within and

across ***skin*** but are also an efficient tool to **permeabilize** the membrane of cells of the ***cutaneous*** or s.c. ***tissue*** . This was shown beneficial for targeting ***cutaneous*** cells with oligonucleotides or genes and might open new opportunities for gene therapy and DNA vaccination. The safety of the application of high- ***voltage*** pulses on ***skin*** was assessed in vivo, using histol. and visual scores, and bioengineering methods. While ***changes*** in ***skin*** ***barrier*** and function were obsd., the irritation was mild and short-lived. Further optimization of the electrode configuration for improved targeting of the stratum corneum should still improve tolerance and levels of sensation.

REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

**L23 ANSWER 6 OF 9 HCAPLUS COPYRIGHT 2006 ACS on STN**

ACCESSION NUMBER: 1993:425456 HCAPLUS <<LOGINID::20060707>>
DOCUMENT NUMBER: 119:25456
**TITLE:** **L-NAME blocks responses to NMDA, substance P and noxious ***cutaneous*** stimuli in cat dorsal horn**
AUTHOR(S): Radhakrishnan, V.; Henry, J. L.
CORPORATE SOURCE: Dep. Physiol., McGill Univ., Montreal, QC, H3G 1Y6, Can.
SOURCE: NeuroReport (1993), 4(3), 323-6
CODEN: NERPEZ; ISSN: 0959-4965
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The NO synthase inhibitor, NG-nitro-L-arginine Me ***ester*** (L-NAME), administered i. ***v*** . (50 mg/kg) or by ***iontophoresis*** , was tested on the responses of spinal dorsal horn neurons in cats anesthetized with .alpha.-choloralose and spinally transected at the L1 level. Extracellular, single-unit recordings were obtained from functionally identified dorsal horn cells. All units included in this study were wide dynamic range neurons. L-NAME reduced the responses of: 12 neurons to noxious thermal stimulation of the receptive field, 9 neurons to noxious pinch, 9 neurons to ***iontophoretic*** application of N-methyl-D-aspartate (NMDA) and (i. ***v*** .), 10 neurons to ***iontophoretic*** application of substance P. The inhibition usually lasted for 50-70 ***min*** following i. ***v*** . administration and for 5-8 ***min*** after ***iontophoretic*** application of L-NAME. The responses of 4 neurons to ***iontophoretic*** application of quisqualate were not affected by L-NAME. The results suggest the possible involvement of NO in the mediation of the spinal effects of NMDA and substance P, and in the transmission of thermal and mech. nociceptive inputs.

**L23 ANSWER 7 OF 9 HCAPLUS COPYRIGHT 2006 ACS on STN**

ACCESSION NUMBER: 1975:119004 HCAPLUS <<LOGINID::20060707>>
DOCUMENT NUMBER: 82:119004
**TITLE:** **Effects of morphine and naloxone on dorsal horn neurons in the cat**
AUTHOR(S): Calvillo, O.; Henry, J. L.; Neuman, R. S.
CORPORATE SOURCE: Dep. Res. Anaesth., McGill Univ., Montreal, QC, Can.
SOURCE: Canadian Journal of Physiology and Pharmacology (1974), 52(6), 1207-11

CODEN: CJPPA3; ISSN: 0008-4212
DOCUMENT TYPE: Journal
LANGUAGE: English
GI For diagram(s), see printed CA Issue.
AB Morphine-HCl (I-HCl) [52-26-6] or I ***sulfate*** [64-31-3], applied by micro**iontophore**sis to functionally identified dorsal horn neurons in segments L5-L7 of cats (chloralose anesthetized, decerebrated, or high spinal), produced primarily a depression of the discharge of neurons responding to noxious radiant heat applied to the ***skin*** . It depressed on-going activity (12 out of 20 neurons), glutamate-evoked excitation, (8/8) and the response to the noxious stimulus (13/21). The response of 2 addnl. neurons to heat was potentiated. The effects began 10-30 sec from the onset of application, reached a max. in up to 8 ***min*** and outlasted application by up to 10 ***min*** . I had relatively little effect on on-going activity and glutamate-evoked excitation of neurons responding to non-noxious stimuli (n = 18). Naloxone-HCl [357-08-4] (i. ***v*** . and ***iontophoretic*** ) reversed these depressions (4/11). I may produce analgesia, at least in part, by a direct action on a specific I receptor in the spinal cord.

**L23 ANSWER 8 OF 9 HCAPLUS COPYRIGHT 2006 ACS on STN**
ACCESSION NUMBER: 1955:85892 HCAPLUS <<LOGINID::20060707>>
DOCUMENT NUMBER: 49:85892
ORIGINAL REFERENCE NO.: 49:16217e-g
**TITLE: Experiments on transpiration. VIII. Duration of action and antisecretory activity of different parasympatholytic drugs examined on the human sweat gland**
AUTHOR(S): Brun, R.; Hunziker, N.
CORPORATE SOURCE: Geneve, Switz.
SOURCE: Dermatologica (1955), 110, 245-53
CODEN: DERAAC; ISSN: 0011-9075
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
AB cf. C.A. 49, 4168f. Parasympatholytic compds. were placed under the ***skin*** of the forearm by ***iontophoresis*** and tested for their ability to inhibit sweating provoked by a subsequent ***iontophoretic*** introduction of pilocarpine. With respect to duration of action, the drugs were effective as follows (in decreasing order): scopolamine (I), Antrenyl (II), atropine (III), Probanthine (IV), banthine ( ***V*** ), Netrine (VI), Prantal (VII), Buscopan (VIII), homatropine (IX). I and II were effective for 3-5 days, while the others persisted for 15-60 ***min*** . From the point of view of activity, the compds. fell in the following order: III, I, II, IV, ***V*** , VI, VII, VIII, IX, multergan.
IT Cyclopentanecarboxylic **acid**, 1-(3,4-xylyl)-
( ***esters*** , effect on perspiration)
IT 50-10-2, Ammonium, diethyl(2-hydroxyethyl)methyl-, bromide, .alpha.-phenylcyclohexaneglycolate 50-34-0, Ammonium, (2-hydroxyethyl)diisopropylmethyl-, bromide, 9-xanthenecarboxylate 50-34-0, 9-Xanthenecarboxylic **acid**, ***ester*** with (2-hydroxyethyl)diisopropylmethylammonium bromide 51-34-3, Scopolamine 62-97-5, Prantal 87-00-3, Homatropine 149-64-4, Buscopan 561-79-5, Netrine 1950-31-8, Ethanol, 2-diethylamino-, 1-(3,4-xylyl)cyclopentanecarboxylate, hydrochloride 412909-21-8,

Scopolammonium, N-butyl-, bromide
(effect on perspiration)
IT 51-55-8, Atropine 62-97-5, Piperidinium, 4-diphenylmethylene-1,1-dimethyl-, methyl ***sulfate***
(effect on sweating)

**L25 ANSWER 5 OF 11 HCAPLUS COPYRIGHT 2006 ACS on STN**
ACCESSION NUMBER: 1998:608281 HCAPLUS <<LOGINID::20060707>>
DOCUMENT NUMBER: 129:306427
**TITLE:** **A pulsed electric field enhances ***cutaneous*** delivery of methylene blue in excised full-thickness porcine ***skin***
AUTHOR(S): Johnson, Patricia G.; Gallo, Stephen A.; Hui, Sek Wen; Oseroff, Allan R.
CORPORATE SOURCE: Departments of Molecular and Cellular Biophysics, Roswell Park Cancer Institute, Buffalo, NY, 14263, USA
SOURCE: Journal of Investigative Dermatology (1998), 111(3), 457-463
CODEN: JIDEAE; ISSN: 0022-202X
PUBLISHER: Blackwell Science, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We used elec. pulses to ***permeabilize*** porcine stratum corneum and demonstrate enhanced epidermal transport of methylene blue, a water-sol. cationic dye. Electrodes were placed on the outer surface of excised full-thickness porcine ***skin*** , and methylene blue was applied to the ***skin*** beneath the pos. electrode; 1 ms pulses of up to 240 ***V*** were delivered at frequencies of 20-100 Hz **for up to 30 ***min*** . The amt. of dye in a ***skin*** sample was detd. from absorbance spectra of dissolved punch biopsy sections. Penetration depth and concn. of the dye were measured with light and fluorescence microscopy of cryosections. At an elec. exposure dose VT (applied ***voltage*** .times. frequency .times. pulse width .times. treatment duration) of about 4700 Vs, there is a threshold for efficient drug delivery. Increasing the applied ***voltage*** or field application time resulted in increased dye penetration. Transport induced by elec. pulses was more than an order of magnitude greater than that seen following ***iontophoresis*** . We believe that the enhanced ***cutaneous*** delivery of methylene blue is due to a combination of de novo ***permeabilization*** of the stratum corneum by elec. pulses, passive diffusion through the ***permeabilization*** sites, and electrophoretic and electroosmotic transport by the elec. pulses. Pulsed elec. fields may have important applications for drug delivery in a variety of fields where topical drug delivery is a goal.
REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

**L25 ANSWER 8 OF 11 HCAPLUS COPYRIGHT 2006 ACS on STN**
ACCESSION NUMBER: 1996:693160 HCAPLUS <<LOGINID::20060707>>
DOCUMENT NUMBER: 126:50899
**TITLE:** ***Transdermal*** ***iontophoretic*** **delivery of insulin using a photoetched microdevice**
AUTHOR(S): Haga, Makoto; Akatani, Mieko; Kikuchi, Jun; Ueno, Yuji; Hayashi, Masahiro
CORPORATE SOURCE: Department of Pharmaceutics, Faculty of Pharmaceutical

Sciences, Science University of Tokyo, Ichigaya, Shinjuku-ku, Tokyo, 162, Japan
SOURCE: Journal of Controlled Release (1997), Volume Date 1996, 43(2,3), 139-149
CODEN: JCREEC; ISSN: 0168-3659
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In order to develop practical ***iontophoretic*** devices for insulin delivery, five types of device, a square type, a square anode with a U-shaped inset cathode-type device (2 divided type), and three types with a square anode, with, resp., 4, 9 and 16 small square inset cathodes (4, 9 and 16 divided types), were fabricated by a photoetching technique, and their effectiveness was examd. in vitro by measuring the ***permeability*** of 6-carboxyfluorescein (6-CF) through the excised abdominal ***skin*** of a nude mouse. All four divided types enhanced the penetration rate of 6-CF more than 16-fold compared with passive diffusion. To test the ***transdermal*** ***iontophoretic*** delivery of insulin in normoglycemic control and diabetic rats, we selected the 2 divided type device, since this pattern was the easiest to fabricate. A significant redn. in blood glucose level (BGL) of 33% after **90 ***min*** of treatment, and a corresponding increase in immunoreactive insulin (IRI) concn. were obsd. in diabetic rats during cathodic d.c. (DC) ***iontophoresis*** (IP) at a const. ***voltage*** of 1.5 ***V*** . The effectiveness of pulsed IP was also studied, but there was no significant difference between DC and pulsed IP in the decrease of BGL. The level of **current** during the initial 10 ***min*** was closely related to the hypoglycemic effect. These findings suggest that some cathodic reaction products may **change** the function of the stratum corneum or that these products may develop a shunt pathway and enhance the ***transdermal*** delivery of aggregated insulin mols. ***Iontophoresis*** -induced ***skin*** damage was also evaluated by measuring impedance **changes**. It was shown that at const.- ***voltage*** IP of 1.5 ***V*** , IP could be carried out for up to 60 ***min*** without any marked effects on the ***skin***.

**L25 ANSWER 9 OF 11 HCAPLUS COPYRIGHT 2006 ACS on STN**
ACCESSION NUMBER: 1994:587089 HCAPLUS <<LOGINID::20060707>>
DOCUMENT NUMBER: 121:187089
**TITLE: ***Iontophoresis*** of a model peptide across human ***skin*** in vitro: effects of ***iontophoresis*** protocol, pH, and ionic strength on peptide flux and ***skin*** impedance**
AUTHOR(S): Craane-van Hinsberg, W. H. M.; Bax, L.; Flinterman, N. H. M.; Verhoef, J.; Junginger, H. E.; Bodde, H. E.
CORPORATE SOURCE: Division of Pharmaceutical Technology, Leiden/Amsterdam Center for Drug Research, Leiden, 2300 RA, Neth.
SOURCE: Pharmaceutical Research (1994), 11(9), 1296-300
CODEN: PHREEB; ISSN: 0724-8741
DOCUMENT TYPE: Journal
LANGUAGE: English
AB This study deals with effects of elec. (c.d., frequency and duty cycle) and chem. (buffer pH and ionic strength) conditions on the flux of the octapeptide, 9-desglycin**amide**, 8-arginine-vasopressin (DGAVP), through

dermatomed human ***skin*** . A pulsed const. **current** was applied during ***iontophoresis*** . The anode faced the anatomical surface of the ***skin*** samples inside the diffusion cells. The resistive and capacitative components of the equiv. elec. circuit of human ***skin*** could be calcd. by fitting the ***voltage*** response to a bi-exponential equation. The ***skin*** resistance prior to ***iontophoresis*** varied between 20 and 60 k.OMEGA..cntdot.cm2. During ***iontophoresis*** a decrease of ***skin*** resistance and an increase of the series capacitances was obsd., which were most pronounced during the first ***hour*** of ***iontophoresis*** ; thereafter both quantities gradually leveled off to an apparent steady state value. The redn. of the resistance during ***iontophoresis*** increased non-linearly with increasing c.d. between 0.013-0.64 mA.cntdot.cm-2. The steady state resistance and capacitances did not vary significantly with frequency and duty cycle of the **current** pulse. There was no pH dependence of ***skin*** resistance at steady state. Between pH 4 and 10, the steady state peptide flux had a bell-shaped pH-dependence with a max. of 0.17 nmol.cntdot.cm-2.cntdot.h-1 at pH 7.4, which is close to the I.E.P. of the peptide. Lowering the ionic strength from 0.15 to 0.015 M NaCl increased the steady state flux at pH 5 and pH 8 by a factor 5 to 0.28 .+-. 0.21 and 0.48 .+-. 0.37 nmol.cntdot.cm-2.cntdot.h-1, resp. Together these observations suggested that DGAVP is transported predominately by vol. flow. At pH 6, at which 65% of the peptide carried a net single pos. charge, the steady-state flux increased with increasing c.d. (0.013-0.64 mA.cntdot.cm-2) from 0.11 .+-. 0.03 to 0.19 .+-. 0.04 nmol.cntdot.cm1-2.cntdot.h-1. ***Skin*** ***permeability*** during passive diffusion preceding ***iontophoresis*** at pH 6.0 was 2.9 .+-. 0.6*10-7 cm.cntdot.h-7. In accordance with theor. predictions based on the Nernst-Planck equation, to which a vol. flow term was added, the flux was proportional to the mean ***voltage*** across the ***skin*** between 0.013 and 0.32 mA.cntdot.cm-2.cntdot.h-1. Variation of frequency or duty cycle did not result in significantly different peptide transport rates. From these studies it is concluded that DGAVP can be transported ***iontophoretically*** through human , ***skin*** . The pH- and ionic strength-dependence of the ***iontophoretic*** peptide flux suggests that transport of DGAVP mainly occurs by vol. flow. Furthermore, the flux of DGAVP appears to be controlled by the applied ***voltage*** rather than by the c.d., as predicted by the Nernst-Planck equation.

**L25 ANSWER 11 OF 11 HCAPLUS COPYRIGHT 2006 ACS on STN**

ACCESSION NUMBER: 1993:567623 HCAPLUS <<LOGINID::20060707>>
DOCUMENT NUMBER: 119:167623
**TITLE:** **Comparison of depolarizing and direct current systems on ***iontophoretic*** enhancement of transport of sodium benzoate through human and hairless rat ***skin*****
AUTHOR(S): Numajiri, Sachihiko; Sakurai, Hidetomo; Sugibayashi, Kenji; Morimoto, Yasunori; Omiya, Harumi; Takenaka, Haruyuki; Akiyama, Noriyoshi
CORPORATE SOURCE: Fac. Pharm. Sci., Josai Univ., Sakado, 350-02, Japan
SOURCE: Journal of Pharmacy and Pharmacology (1993), 45(7), 610-13
CODEN: JPPMAB; ISSN: 0022-3573
DOCUMENT TYPE: Journal

LANGUAGE: English

AB A d.c. system and a pulsed depolarization (PD) system were evaluated for their ***iontophoretic*** permeation of sodium benzoate, as a model drug, through hairless rat and human ***skin*** . Approx. the same initial permeation of sodium benzoate through the hairless rat ***skin*** was obtained at 0.1 mA for the d.c. device and at 3.0 mA for the PD device. A study of the drug permeation was performed using a two-chamber ***iontophoretic*** diffusion cell, over 2 cycles of 3 successive on-off exptl. conditions [stage I (off) 0-4 h, II (on) 4-6 h, III (off) 6-10 h, saline washings 10-24 h, IV (off) 24-28 h, ***V*** (on) 28-30 h and VI (off) 30-34 h]. The ***skin*** permeation rate during stage IV of the ***iontophoresis*** as compared with the control group through hairless rat or human ***skin*** for the DC system was 2-4-fold that in stage I, whereas in the same stage using the PD system it was almost the same as in stage I. Impedance of ***skin*** decreased during the application of either system (stage II); however, the value significantly recovered during stage III only in the case of the PD system use on human ***skin*** . Histol. observation revealed no ***tissue*** **alter**ation in the hairless rat ***skin*** after using either system. When the d.c. or PD system was applied to volunteers, the ***min*** . c.d. producing pain was 0.016 or 2.7 mA cm-2, resp. The PD system was more appropriate for ***iontophoresis*** application than the d.c. system from the point of view of ***skin*** ***permeability*** of the drug and effect on the ***skin*** .

ST depolarizing ***iontophoresis*** ***skin*** transport sodium benzoate; direct **current** ***iontophoresis*** ***skin*** transport benzoate

IT Biological transport
(of sodium benzoate, by human and rat ***skin*** , ***iontophoretic*** enhancement of, depolarizing and d.c. systems effect on)

IT ***Iontophoresis***
(sodium benzoate transport through human and rat ***skin*** enhancement by, depolarizing and d.c. systems effect on)

IT ***Skin***
(sodium benzoate transport through human and rat, ***iontophoretic*** enhancement of, depolarizing and d.c. systems effect on)

IT Electric **current**
(depolarization, ***iontophoresis*** permeation of sodium benzoate through ***skin*** by using)

IT Electric **current**
(direct, ***iontophoresis*** permeation of sodium benzoate through ***skin*** by using)

IT 65-85-0, Benzoic **acid**, biological studies 532-32-1
RL: BIOL (Biological study)
(biol. transport of, by human and rat ***skin*** , ***iontophoretic*** enhancement of, depolarizing and d.c. systems effect on)

**Basic Search**

Advanced Search Search Preferences

iontophoresis AND voltage AND ("alternating current") Search

☑ Journal sources ☑ Preferred Web sources ☑ Other Web sources ☐ Exact phrase

Searched for:: :All of the words:**iontophoresis** AND **voltage** AND (**"alternating current"**) AND (**enhancer**)

Found:: :**10 total** | **1 journal results** | **9 preferred web results** | **0 other web results**

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☐ **1.** Transdermal iontophoresis revisited
**Panchagnula, R. / Pillai, O. / Nair, V.B. / Ramarao, P.**, *Current Opinion in Chemical Biology*, Aug 2000
...flux achieved with **iontophoresis** alone [20,21] . Therefore...decided by the chemical **enhancer**, rather than **iontophoresis** [22] . An interesting...is the use of high **voltage** pulses for a short...followed by conventional **iontophoresis** with lesser current...combination of chemical **enhancers** and **iontophoresis**...
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☐ **2.** MICROPORATION OF TISSUE FOR DELIVERY OF BIOACTIVE AGENTS
**EPPSTEIN, Jonathan, A. / ALTEA TECHNOLOGIES, INC.**, *PATENT COOPERATION TREATY APPLICATION*, Jul 1998
...penetration or chemical **enhancers**. Chemical **enhancers** are well known...skin to drugs is **iontophoresis**. Iontophoresis...by passing an **alternating current** through the material...chemical permeation **enhancers** are used to increase...
**Full text available at patent office. For more in-depth searching go to** LexisNexis
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similar results

☐ **3.** Advancing women, a business issue
**Hilts, Bonnie Rae**, Jan 2000
...skin anesthesia can be produced by **iontophoresis** of local anesthetic drugs. Moreover...A-4,764,164 discloses a device for **iontophoresis** including an electric source, a...means for generating a low-frequency **voltage** with a ratio of positive **voltage**...means to apply said low-frequency **voltage** to a human body. Briefly, and in...other undesirable effects during **iontophoresis**. In attempting to replicate the...
**Full text thesis available via NDLTD**
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☐ **4.** IONTOPHORETIC TREATMENT SYSTEM
**Tapper, Robert / Tapper, Robert**, *EUROPEAN PATENT*, Nov 1998
...skin anesthesia can be produced by **iontophoresis** of local anesthetic drugs. Moreover...A-4,764,164 discloses a device for **iontophoresis** including an electric source, a...means for generating a low-frequency **voltage** with a ratio of positive

**voltage**...means to apply said low-frequency **voltage** to a human body. Briefly, and in...other undesirable effects during **iontophoresis**. In attempting to replicate the...
**Full text available at patent office. For more in-depth searching go to** LexisNexis
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☐ **5.** COMPOUNDS WITH PTH ACTIVITY AND RECOMBINANT DNA VECTORS ENCODING SAME
**OLDENBURG, Kevin, R. / SELICK, Harold, E. / AFFYMAX TECHNOLOGIES N.V.**, *PATENT COOPERATION TREATY APPLICATION*, May 1995
...been transformed by a recombinant DNA vector. For purposes of the present invention, procaryotic host cells are preferred. "**Iontophoresis**" or "iontophoretic" refers to the introduction of an ionizable chemical through skin or mucous membranes by the application...
**Full text available at patent office. For more in-depth searching go to** LexisNexis
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☐ **6.** ELECTROTRANSPORT DEVICE COMPRISING BLADES
**SUN, Ying / OAKESON, Ralph, W. / WISNIEWSKI, Stephen, J. / WANG, Jonas, C., T. / NIEMIEC, Susan, M. / JOHNSON & / JOHNSON CONSUMER COMPANIES, INC.**, *PATENT COOPERATION TREATY APPLICATION*, Mar 2000
...through the skin barrier, namely, **iontophoresis**, electro-osmosis and electroporation. In transdermal **iontophoresis**, an ionized drug migrates into the...extremely short pulses of high electric **voltage** and low current. These methods are...pathways by!:e lectrotransport', e.g., **iontophoresis**. In one embodiment, liposomal formulations...
**Full text available at patent office. For more in-depth searching go to** LexisNexis
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☐ **7.** COMPOSITIONS AND METHODS FOR TRANSDERMAL DRUG DELIVERY
**SELICK, Harold, E. / OLDENBURG, Kevin, R. / AFFYMAX TECHNOLOGIES N.V.**, *PATENT COOPERATION TREATY APPLICATION*, Aug 1994
...al. (1987) "Penetration **Enhancerl˜** in Transdermal Delivery...Various forms of chemical **enhancers**, such as those enhancing...This technique, known as **iontophoresis**, uses electrostatic forces...rate of drug delivery in **iontophoresis** is directly proportional...electrical energy of sufficient **voltage** and duration to produce...
**Full text available at patent office. For more in-depth searching go to** LexisNexis
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☐ **8.** IONTOPHORETIC TREATMENT SYSTEM
**TAPPER, Robert / TAPPER, Robert**, *PATENT COOPERATION TREATY APPLICATION*, Aug 1997
...skin anesthesia can be produced by **iontophoresis** of local anes- thetic drugs. Moreover...other undesir- able effects during **iontophoresis**. In attempting to replicate the...delivery with relatively lower driving **voltage**. This process incre
**Full text available at patent office. For more in-depth searching go to** LexisNexis
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☐ **9.** COMPOSITIONS AND METHODS FOR ENHANCED DRUG DELIVERY
**HALE, Ron, L. / LU, Amy / SOLAS, Dennis / SELICK, Harold, E. / OLDENBURG, Kevin, R. / ZAFFARONI, Alejandro, C. / AFFYMAX TECHNOLOGIES N.V.**, *PATENT COOPERATION TREATY APPLICATION*, Dec 1993
...et al. (1987) "Penetration **Enhancers**", in Transdermal Delivery...Various forms of chemical **enhancers**, such as those enhancing...This technique, known as **iontophoresis**, uses an electric field to...The rat of drug delivery in **iontophoresis** is directly proportional...
**Full text available at patent office. For more in-depth searching go to** LexisNexis

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☐ **10.** TRANSPORT OF MOLECULES ACROSS TISSUE USING ELECTROPORATION
**WEAVER, James, C. / POWELL, Kevin, T. / LANGER, Robert, S., Jr. / MASSACHUSETTS INSTITUTE OF TECHNOLOGY**, *EUROPEAN PATENT*, Nov 1990
...through the use of absorption **enhancers**. These are generally penetrating...skin. An example of one such **enhancer** is dimethyl sulfoxide (DMSO...enzymes are subjected to a high **voltage** pulse of short duration...US-A-4 702 732 discloses **iontophoresis** apparatus in which electrical...is caused by short, high **voltage** electrical pulses applied...
**Full text available at patent office. For more in-depth searching go to** LexisNexis
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File 350:Derwent WPIX 1963-2006/UD,UM &UP=200642
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Set     Items   Description
S1        499   AU='MILLER D' OR AU='MILLER D J'
S2        153   AU='MILLER DAVID' OR AU='MILLER DAVID J':AU='MILLER DAVID -
            JONATHAN'
S3         23   AU='HIGUCHI W' OR AU='HIGUCHI W I' OR AU='HIGUCHI WILLIAM'
            OR AU='HIGUCHI WILLIAM I'
S4        888   AU='LI K'
S5         10   AU='LI KEVIN' OR AU='LI KEVIN S'
S6         13   AU='LI K S' OR AU='LI K.S.'
S7         13   AU='FLYNN G' OR AU='FLYNN G L'
S8          6   AU='FLYNN GORDON L'
S9       4651   IONTOPHORESIS
S10        19   S1:S8 AND S9
S11        19   IDPAT (sorted in duplicate/non-duplicate order)
S12        14   IDPAT (primary/non-duplicate records only)

12/3,AB,IC/6     (Item 6 from file: 350)
DIALOG(R)File 350:Derwent WPIX
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015543514
WPI Acc No: 2003-605670/200357
Related WPI Acc No: 2001-557631; 2001-565338
XRAM Acc No: C03-164792
XRPX Acc No: N03-482852
  Increasing battery life of alternating current iontophoretic device,
  involves applying alternating current to body tissue, and delivering
  barrier modifying agent prior to and/or during current application
Patent Assignee: FLYNN G L (FLYN-I); HIGUCHI W I (HIGU-I); LI K (LIKK-I);
  MILLER D J (MILL-I)
Inventor:  FLYNN G L ;  HIGUCHI W I ;  LI K ;  MILLER D J
Number of Countries: 001  Number of Patents: 001
Patent Family:
Patent No     Kind   Date     Applicat No    Kind   Date     Week
US 20020161323  A1  20021031  US 2001783138   A   20010213  200357  B
                            US 2001783696   A   20010213
                            US 200114741    A   20011210
Priority Applications (No Type Date): US 200114741 A 20011210; US
  2001783138 A 20010213; US 2001783696 A 20010213
Patent Details:
Patent No  Kind Lan Pg   Main IPC    Filing Notes
US 20020161323 A1    36 A61N-001/30   CIP of application US 2001783138
                                      CIP of application US 2001783696
Abstract (Basic): US 20020161323 A1
Abstract (Basic):
        NOVELTY - Increasing battery life of an alternating current
    iontophoretic device comprises applying alternating current to a
    localized body tissue with an inherent barrier limiting the transport
    of compounds. Barrier modifying agent to change the barrier, is
    delivered to the region prior to and/or during current application, to
    reduce voltage required to achieve and maintain a target resistance
```

level.

DETAILED DESCRIPTION - Increasing battery life of an alternating current iontophoretic device comprises applying an alternating current (AC) to a localized region of body tissue having an inherent barrier limiting the transport of compounds. The AC is generated using an AC iontophoretic device and is applied at a level sufficient to decrease the electrical resistance of the tissue to a target resistance level and to maintain the electrical resistance of the tissue at the target level. An amount of at least one barrier modifying agent effective to alter the penetration barrier, is delivered to the localized region prior to and/or during current application, to reduce the voltage level required to achieve and maintain the target resistance level to facilitate transport of a compound across the tissue.

An INDEPENDENT CLAIM is included for an AC **iontophoresis** device having electrode assemblies (I, II), and an AC source electrically connected to the assemblies. Assembly (I) is adapted to receive an analyte and be placed in ion conducting and analyte receiving relation with respect to the localized region. The assembly has a reservoir for collecting and containing an analyte extracted from the patient's body beneath the localized region. Assembly (II) is adapted to be placed in ion transmitting relation with the tissue at a location spaced apart from assembly (I). The current source applies an AC to the localized region of tissue at a level sufficient to achieve and maintain a target electrical resistance within the tissue. At least one assembly comprises a barrier modifying agent for delivery to the localized region of the tissue. The agent reduces the voltage required to achieve and maintain the target electrical resistance.

USE - Used for increasing the battery life of an alternating current iontophoretic device used to transport a compound through a localized region of body tissue e.g. in drug administration, glucose monitoring, therapeutic drug monitoring, detoxification methods, in pain management, metabolite monitoring and dermatological treatment. The compound is an analyte comprising glucose, an amino acid, a marker of a disease state, substance of abuse, electrolyte, mineral, hormone, peptide, metal ion, nucleotidic material, gene and/or enzyme, especially e.g. analgesic agents, anticancer agents and anesthetic agents.

ADVANTAGE - The method allows the maintenance of a constant electrical state in a localized region of the tissue through which transport occurs, allowing a compound to be transported across the tissue controllably and predictably. The barrier modifying agent reduces the time and the voltage level required to achieve a target electrical resistance, reducing patient discomfort and increasing the battery life of the **iontophoresis** device. The method can be used with a variety of tissues, including both animal and plant tissues. The application of barrier modifying agent reduces the amount of current required to achieve and sustain electroporation.

pp; 36 DwgNo 0/13
International Patent Class (Main): A61N-001/30

**12/3,AB,IC/12 (Item 12 from file: 349)**
DIALOG(R)File 349:PCT FULLTEXT

00827203
**METHODS FOR DELIVERING AGENTS USING ALTERNATING** CURRENT

**PROCEDE D'APPORT D'AGENTS AU MOYEN DE COURANT ALTERNATIF**
Patent Applicant/Assignee:
UNIVERSITY OF UTAH RESEARCH FOUNDATION, Technology Transfer Office, Suite 110, 615 Arapeen Drive, Salt Lake City, UT 84108, US, US (Residence), US (Nationality)
Inventor(s):
LI S Kevin, 659 South 1200 East #1C, Salt Lake City, UT 84102, US,
**HIGUCHI William I** , 342 East Capitol Park Avenue, Salt Lake City, UT 84103, US,
ZHU Honggang, 1909 East Sunnyside Avenue #340, Salt Lake City, UT 84108, US
SONG Yang, 1909 East Sunnyside Avenue #539, Salt Lake City, UT 84108, US
Legal Representative:
AUSENHUS Scott L (et al) (agent), Townsend and Townsend and Crew LLP, Two Embarcadero Center, 8th Floor, San Francisco, CA 94111, US,
Patent and Priority Information (Country, Number, Date):
Patent: WO 200160449 A1 20010823 (WO 0160449)
Application: WO 2001US4654 20010213 (PCT/WO US0104654)
Priority Application: US 2000184119 20000218; US 2000244116 20001028
Designated States:
(Protection type is "patent" unless otherwise stated - for applications prior to 2004)
AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
(EP) AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR
(OA) BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG
(AP) GH GM KE LS MW MZ SD SL SZ TZ UG ZW
(EA) AM AZ BY KG KZ MD RU TJ TM
Main International Patent Class (v7): A61N-001/32
Publication Language: English
Filing Language: English
Fulltext Word Count: 13656
English Abstract
A variety of methods for transporting different agents such as pharmaceutical agents, nutrients and genetic materials across a tissue are provided. The methods utilize an AC signal to maintain a substantially constant electrical state in a region of the tissue through which transport occurs, thereby allowing agent to be transported across the tissue in a controlled and predictable manner. Certain methods include an optional AC or DC prepulse signal to initially achieve the target electrical state. An optional DC offset signal can also be included to assist in promoting transfer of the agent. The methods have utility in a variety of different clinical settings and applications.

**12/3,AB/3 (Item 1 from file: 350)**
DIALOG(R)File 350:Derwent WPIX

016170643
WPI Acc No: 2004-328530/200430
**Formulation for treating posterior ocular pathologies, comprises a compound and a component for** enhancing **transport of the compound across the sclera of the eye and/or a component for prolonging residence of the compound within the eye**
Patent Assignee: HIGUCHI W (HIGU-I); LI S K (LISK-I); MILLER D J (MILL-I)

Inventor: HIGUCHI W; LI S K; MILLER D J
Number of Countries: 001 Number of Patents: 001
Patent Family:

| Patent No | Kind | Date | Applicat No | Kind | Date | Week | |
|---|---|---|---|---|---|---|---|
| US 20040071761 | A1 | 20040415 | US 2002269911 | A | 20021011 | 200430 | B |

Priority Applications (No Type Date): US 2002269911 A 20021011
Patent Details:

| Patent No | Kind | Lan | Pg | Main IPC | Filing Notes |
|---|---|---|---|---|---|
| US 20040071761 | A1 | | 16 | A61K-031/137 | |

Abstract (Basic): US 20040071761 A1

NOVELTY - A pharmaceutical formulation comprises a therapeutic compound (A) and a component (I) for **enhancing** the transport of (A) across the sclera of the eye toward and into an intermediate and/or a posterior portion of the eye and/or a component (II) for prolonging the residence time of (A) within the intermediate and posterior portions of the eye.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following:

(a) an ophthalmic device (D) for topical delivery of (A) to a posterior region of eye comprising: a fluid retaining member, (A) releasably associated with the fluid retaining member, and (I) and/or (II);

(b) increasing the concentration of (A) in a posterior region of the eye involving: (i) administering (A); and (ii) additionally administering (I) and/or (II); and

(c) achieving an effect in a posterior retinal region of a subject involving: steps (i) and (ii); or placing the device (D) on an eye of the patient, and administering (A) and (I) and/or (II) to the eye.

ACTIVITY - Ophthalmological; Antidiabetic; Virucide; Antibacterial; Antifungal; Cytostatic; Neuroprotective.

MECHANISM OF ACTION - None given.

USE - For treatment of posterior ocular pathology (claimed) e.g. age related macular degeneration, diabetic retinopathy, bacterial endophthalmitis, bacterial retinitis, fungal retinitis, viral retinitis, eye cancer, glioblastomas, bacterial, viral and fungal infections; posterior and intermediate uveitis and glaucomatous degeneration of optic nerve.

ADVANTAGE - The composition increases the concentration of the therapeutic compound in an intermediate and posterior ocular regions of the eye by increasing the efficiency and efficacy of the delivery of the drug by passive delivery through conjunctiva and sclera, to the posterior region of the eye and achieves an increased efficiency and efficacy of the therapeutic effect in the intermediate and posterior regions of the eye; without the potential risks and side effects associated with the systemic and injectable delivery methods. The composition further decreases the frequency of the treatment.

pp; 16 DwgNo 0/3

Derwent Class: B05; D16
International Patent Class (Main): A61K-031/137
International Patent Class (Additional): A61K-009/70

**12/3,AB/5 (Item 2 from file: 350)**
DIALOG(R)File 350:Derwent WPIX

015646192

WPI Acc No: 2003-708375/200367
**Decreasing flux variability in** iontophoretic **device to transport compound through body** tissue **such as** skin **, by applying current to** tissue **to transport compound and applying polyelectrolyte to stabilize flux rate of compound**
Patent Assignee: HASTINGS M S (HAST-I); HIGUCHI W I (HIGU-I); LI S K (LISK-I); MILLER D J (MILL-I)
Inventor: HASTINGS M S; HIGUCHI W I; LI S K; MILLER D J
Number of Countries: 001 Number of Patents: 001
Patent Family:

| Patent No | Kind | Date | Applicat No | Kind | Date | Week | |
|---|---|---|---|---|---|---|---|
| US 20030065305 | A1 | 20030403 | US 2001911594 | A | 20010723 | 200367 | B |
| | | | US 2002226622 | A | 20020821 | | |

Priority Applications (No Type Date): US 2002226622 A 20020821; US 2001911594 A 20010723
Patent Details:

| Patent No | Kind | Lan | Pg | Main IPC | Filing Notes |
|---|---|---|---|---|---|
| US 20030065305 | A1 | | 21 | A61N-001/30 | CIP of application US 2001911594 |

Abstract (Basic): US 20030065305 A1

NOVELTY - A method for decreasing flux variability in an **iontophoretic** device used to transport a compound through a localized region of a patient's body **tissue** , involves applying a current to the body **tissue** to transport the compound and applying polyelectrolyte either before and/or during application of the current, to body **tissue** for stabilizing the flux rate of compound through the body **tissue.**

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for a method for decreasing lag time of the **iontophoretic** of a compound through a localized region of a patient's body **tissue** , which involves applying a current to the localized region of body **tissue** to transport the compound and applying polyelectrolyte either before and/or during application of the current, to body **tissue** for stabilizing the flux rate of compound through the body **tissue** .

USE - For decreasing flux variability in **iontophoretic** device to transport therapeutic compounds such as beta-agonist, analeptic **agents** , analgesic **agents** , anesthetic **agents** , anti-angiogenic **agents** , anti-arthritic **agents** , anti-asthmatic **agents** , antibiotics, anticancer **agents** , etc., through the body **tissue** such as **skin** , ocular **tissue** e.g. conjunctiva, sclera and cornea and **mucosal tissue** (claimed).

ADVANTAGE - The method effectively reduces the lag time of **iontophoretic** systems and improves the increased level of permeant transport in electro-osmosis without any irritation, sensitization and pain. The method improves the accuracy, reproducibility and precision. The method provides control delivery of insulin or other hyperglycemic **agents** , thereby the method also used to treat a various disorders such as diabetes.

pp; 21 DwgNo 0/0
Derwent Class: A96; B07; D22; P34; S05
International Patent Class (Main): A61N-001/30

**12/3,AB/8 (Item 8 from file: 350)**
DIALOG(R)File 350:Derwent WPIX

015187557 **Image available**
WPI Acc No: 2003-248091/200324

**Device that increases analyte flux during reverse** iontophoresis **conducted on region** of body tissue **e.g., skin , has electrode assembly comprising polyelectrolyte composition that cannot be transported into body** tissue
Patent Assignee: ACIONT INC (ACIO-N); HIGUCHI W I (HIGU-I)
Inventor: HIGUCHI W I
Number of Countries: 100 Number of Patents: 003
Patent Family:

| Patent No | Kind | Date | Applicat No | Kind | Date | Week |
|---|---|---|---|---|---|---|
| WO 200310538 | A1 | 20030206 | WO 2002US23428 | A | 20020722 | 200324 B |
| US 20030065285 | A1 | 20030403 | US 2001911594 | A | 20010723 | 200325 |
| AU 2002329628 | A1 | 20030217 | AU 2002329628 | A | 20020722 | 200452 |

Priority Applications (No Type Date): US 2001911594 A 20010723
Patent Details:

| Patent No | Kind | Lan | Pg | Main IPC | Filing Notes |
|---|---|---|---|---|---|
| WO 200310538 | A1 | E | 34 | G01N-033/52 | |

Designated States (National): AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG UZ VN YU ZA ZM ZW
Designated States (Regional): AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SK SL SZ TR TZ UG ZM ZW

| | | | |
|---|---|---|---|
| US 20030065285 | A1 | A61N-001/30 | |
| AU 2002329628 | A1 | G01N-033/52 | Based on patent WO 200310538 |

Abstract (Basic): WO 200310538 A1

NOVELTY - An **iontophoresis** device (I) comprising a first electrode assembly (E1) with a reservoir for collecting and containing analyte extracted from body, and polyelectrolyte composition; a second electrode assembly (E2) placed at a location spaced apart from (E1); and an electrical current source, electrically connected to (E1) and (E2), is new.

DETAILED DESCRIPTION - An **iontophoresis** device (I) that increases analyte flux during reverse **iontophoresis** conducted on a region of body **tissue** comprises a first electrode assembly (E1) adapted to be placed in ion conducting and analyte receiving relation with the body **tissue** comprising a reservoir for collecting and containing an analyte extracted from the body, and a first polyelectrolyte composition; a second electrode assembly (E2) adapted to be placed in ion transmitting relation with the body **tissue** at a location spaced apart from (E1); and an electrical current source, electrically connected to (E1) and (E2).

INDEPENDENT CLAIMS are also included for:

(1) extracting an analyte from a region of body **tissue** , involves placing in contact with the body **tissue** a first electrode assembly comprising an electrically conducting medium comprising a first polyelectrolyte composition that cannot be readily transported into and through the body **tissue** when an electrical current is applied, placing in contact with the body **tissue** a second electrode assembly adapted to be placed in ion transmitting relation with the body surface at a location spaced apart from the first electrode assembly, and applying the electrical current across the region of body **tissue** by the first and second electrode assemblies, with a voltage and duration effective to induce electro-osmosis and transport the analyte to the first electrode assembly; and

(2) an improved method for extracting an analyte from a region of body **tissue** , involves placing the first and second electrode

assemblies on an individual's body surface in ion-transmitting relation to it, first and second electrode assemblies spaced apart at a selected distance, and applying an electrical current across the region of body **tissue** by first and second electrode assemblies, with a voltage and duration effective to induce electroosmosis and transport the analyte to first electrode assembly at a transport rate having a mean steady state **permeability** that varies when the method is applied to different regions of body **tissue** , the improvement comprising incorporating a polyelectrolyte composition into the first electrode assembly that exhibits significantly impeded transport into the body **tissue** when electrical current is applied, the polyelectrolyte composition effective to provide a substantial decrease in the variability of mean steady state **permeability** when the method is applied to different regions of body **tissue** .

USE - (I) is useful in any condition where a compound is removed from the body by **iontophoresis** , such as glucose monitoring, phenylalanine monitoring, therapeutic drug, fertility monitoring, monitoring for illicit drug use, noninvasive pharmacokinetic or toxicokinetic monitoring and monitoring of any other body component, endogenous or introduced, that is a marker of health or disease.

ADVANTAGE - The device increases electroosmotic solvent flow and therefore, noninvasive extraction of uncharged permeant molecules through the **skin** . By replacing the mobile co-ions, which are capable of easily entering the pores from the receiver compartment of a reverse **iontophoretic** extraction device with large conductive polyelectrolyte within the reservoir that do not appreciably enter the pores, the device significantly improves the amount of analyte extracted, improves device performance, decreases energy requirements, increases battery life, reduces the potential for irritation, and improves accuracy, reproducibility and precision. The device and the method reduce changes in flux encountered during **iontophoresis** as well as reduce intersubject variability.

DESCRIPTION OF DRAWING(S) - The figure shows the schematic diagram of electroosmotic transport using **iontophoretic** device comprising a polyelectrolyte composition.

pp; 34 DwgNo 2/3

Derwent Class: B04; D16; P34; S03; S05
International Patent Class (Main): A61N-001/30; G01N-033/52
International Patent Class (Additional): A61N-001/30

**12/3,AB/7 (Item 7 from file: 350)**
DIALOG(R)File 350:Derwent WPIX

015513857 **Image available**
WPI Acc No: 2003-576004/200354
**Iontophoresis device for minimizing changes in active agent flux, comprises first electrode assembly placed in agent transmitting relation, second electrode assembly placed in ion transmitting relation and electrical current**
Patent Assignee: ACIONT INC (ACIO-N)
Inventor: HIGUCHI W I; LI K; MILLER D J
Number of Countries: 001 Number of Patents: 001
Patent Family:

| Patent No | Kind | Date | Applicat No | Kind | Date | Week | |
|---|---|---|---|---|---|---|---|
| US 6553255 | B1 | 20030422 | US 2000698697 | A | 20001027 | 200354 | B |

Priority Applications (No Type Date): US 2000698697 A 20001027

Patent Details:
Patent No Kind Lan Pg Main IPC Filing Notes
US 6553255 B1 17 A61N-001/30
Abstract (Basic): US 6553255 B1

NOVELTY - **Iontophoresis** device comprises an electrode assembly-I (EA-I) placed in **agent** transmitting relation with body **tissue** comprising active **agent** and at least one background co-ion having hindrance factor, electrode assembly-II (EA-II) placed in ion transmitting relation with the body surface spaced apart from EA-I and electrical **current** source connecting to EA-I and EA-II.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

(1) delivering active **agent** across body **tissue** using electrical **current**, which comprises placing a composition comprising the active **agent** and at least one background co-ion having hindrance factor in contact with the body **tissue** and applying electrical **current** to the region of **tissue** , with the **current** of a **voltage** and duration effective to induce electroporation of the body surface in **tissue** , and

(2) extracting an analyte permeant **agent** across body **tissue** using electrical **current**, which comprises transporting at least one background ion having a hindrance factor that changes at a faster rate than the hindrance factor of the co-ion of the analyte in the body, at the same time and in different directions of analyte, with changes in permeant flux minimized and inter**tissue** variability reduced.

USE - Used for minimizing changes in the permeant flux and reducing inter**tissue** variability in the **tissue** such as **skin** and **mucosal tissue** (claimed).

ADVANTAGE - The device minimizes the changes in active **agent** flux and reduces inter**tissue** variability in the **tissue** .

DESCRIPTION OF DRAWING(S) - The figure shows a schematic diagram of the **iontophoretic** drug delivery.

pp; 17 DwgNo 1a/5

Derwent Class: B05; B07; D16; D22; P34; S05
International Patent Class (Main): **A61N-001/30**

**12/TI/1 (Item 1 from file: 350)**
DIALOG(R)File 350:(c) 2006 The Thomson Corp. All rts. reserv.
**Iontophoretic device for use in e.g. human, has electrode assemblies with distance from one another to control location of sustained release depot formed in-vivo when active agent and depot forming agent are delivered to subject**

**12/TI/2 (Item 2 from file: 350)**
DIALOG(R)File 350:(c) 2006 The Thomson Corp. All rts. reserv.
**Iontophoretic method for transporting compound of interest, involves applying current to localized region, such that compound is transported iontophoretically via localized region while hindering transport of competing ion**

**12/TI/4 (Item 4 from file: 350)**
DIALOG(R)File 350:(c) 2006 The Thomson Corp. All rts. reserv.
**Compound iontophoretically transporting-device includes reference electrode in conjunction with at least one of two iontophoretic electrodes to monitor and control electrical resistance of body tissue at localized region**

**12/TI/9 (Item 9 from file: 350)**
DIALOG(R)File 350:(c) 2006 The Thomson Corp. All rts. reserv.

**Increasing permeability of biological membranes e.g. skin - by exposure to ultrasound at above esp. 10MHz to enhance transdermal drug delivery**

**12/TI/10 (Item 10 from file: 348)**
DIALOG(R)File 348:(c) 2006 European Patent Office. All rts. reserv.
**METHOD AND APPARATUS FOR INCREASING, FLUX DURING REVERSE** IONTOPHORESIS

**12/TI/11 (Item 11 from file: 349)**
DIALOG(R)File 349:(c) 2006 WIPO/Univentio. All rts. reserv.
**METHODS AND DEVICES FOR SUSTAINED IN-VIVO RELEASE OF AN ACTIVE AGENT**

**12/TI/13 (Item 13 from file: 349)**
DIALOG(R)File 349:(c) 2006 WIPO/Univentio. All rts. reserv.
**METHODS FOR EXTRACTING SUBSTANCES USING ALTERNATING CURRENT**

**12/TI/14 (Item 14 from file: 349)**
DIALOG(R)File 349:(c) 2006 WIPO/Univentio. All rts. reserv.
**TOPICAL COMPOSITIONS COMPRISING THALIDOMIDE FOR THE TREATMENT OF INFLAMMATORY DISEASES**

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File 155:MEDLINE(R) 1950-2006/Jul 05
         (c) format only 2006 Dialog
File  73:EMBASE 1974-2006/Jul 06
         (c) 2006 Elsevier Science B.V.
File   2:INSPEC 1898-2006/Jun W4
         (c) 2006 Institution of Electrical Engineers
File  34:SciSearch(R) Cited Ref Sci 1990-2006/Jun W4
         (c) 2006 Inst for Sci Info
File 434:SciSearch(R) Cited Ref Sci 1974-1989/Dec
         (c) 1998 Inst for Sci Info
Set     Items   Description
S1      39574   AU=(MILLER D? OR MILLER, D? OR HIGUCHI W? OR HIGUCHI, W? OR
              LI K? OR LI, K? OR FLYNN G? OR FLYNN, G?)
S2      20737   IONTOPHORE?
S3        114   S1 AND S2
S4     118658   BATTERY OR BATTERIES
S5          0   S3 AND S4
S6     731074   VOLT????
S7     189565   AC OR ALTERNATING()CURRENT? ?
S8         54   S3 AND S6
S9         28   S3 AND S7
S10        17   S8 AND S9
S11         7   RD  (unique items)

 11/9/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2006 Dialog. All rts. reserv.
15321712   PMID: 15637683
   Effects of electrophoresis and electroosmosis during  alternating
 current  iontophoresis  across human epidermal membrane.
  Yan Guang; Peck Kendall D; Zhu Honggang;  Higuchi William I ; Li S Kevin
  University of Utah, Department of Pharmaceutics and Pharmaceutical
Chemistry, 30 S 2000 E, Skaggs Hall 213, Salt Lake City, Utah 84112, USA.
  Journal of pharmaceutical sciences (United States)  Mar 2005,  94  (3)
 p547-58,  ISSN 0022-3549--Print  Journal Code: 2985195R
  Contract/Grant No.: GM 063559; GM; NIGMS
  Publishing Model Print
  Document type: Journal Article
  Languages: ENGLISH
  Main Citation Owner: NLM
  Record type: MEDLINE; Completed
  Subfile:   INDEX MEDICUS
  Previous studies in our laboratory have demonstrated that skin electrical
resistance  can be controlled by an  alternating  current  ( AC ) electric
field.  By  maintaining  constant skin resistance,  AC  iontophoresis  has
been  shown  to  reduce  the  iontophoretic  flux  variability of neutral
permeants.  Recently,  it  was  found that symmetric square-wave  AC  could
enhance  iontophoretic  transport  of both neutral and ionic permeants by
means  of  electrophoresis  and/or  electroosmosis  in a synthetic membrane
system, and a model was presented to describe the experimental results. The
objective  of  the present study was to assess the effects of  AC  voltage
and  frequency  and  direct  current (DC) offset on the flux of neutral and
ionic model permeants with human epidermal membrane (HEM). Experiments were
conducted  under  two  different  conditions:  constant  AC  voltage
 iontophoresis  and  iontophoresis  using constant HEM resistance with DC
offset  voltage  . The following are the main findings in these experiments.
```

In the constant **AC voltage** study, when the permeability data were compared at the same HEM electrical resistance, it was demonstrated that **AC** even at high frequency (approximately 1 kHz) could enhance the transport of the ionic permeant (tetraethylammonium ion) across HEM, but no enhancement was observed for the neutral permeant (arabinose). For the ionic permeant flux enhancement, the higher the applied **AC voltage** , the greater the flux enhancement. There was little or no **AC** frequency dependence of the flux enhancement in the frequency range of 50-1000 Hz. In the constant HEM resistance study of **AC** with DC offset, approximately linear relationships were observed between flux enhancement and the DC offset **voltage** for both the neutral and ionic permeants, and these results were found to be consistent with predictions of the modified Nernst-Planck model for conventional constant **voltage** DC **iontophoresis** . When the DC offset **voltage** was increased, the **AC** component of the flux enhancement for the ionic permeant decreased, eventually appearing to contribute negligibly to the total flux enhancement at high DC offset **voltages** . 

Descriptors: *Epidermis--metabolism--ME; * **Iontophoresis** --methods--MT; Comparative Study; Electrophoresis--methods--MT; Humans; In Vitro; Osmosis; Research Support, N.I.H., Extramural; Research Support, U.S. Gov't, P.H.S.

Record Date Created: 20050207

Record Date Completed: 20050721

**11/9/2 (Item 2 from file: 155)**

DIALOG(R)File 155:MEDLINE(R)



15154993 PMID: 15459891

**Quantitative study of electrophoretic and electroosmotic enhancement during** alternating current iontophoresis **across synthetic membranes.**

Yan Guang; Li S Kevin; Peck Kendall D; Zhu Honggang; **Higuchi William I**

Department of Pharmaceutics and Pharmaceutical Chemistry, University of Utah, 30 S 2000 E, Skaggs Hall 213, Salt Lake City, Utah 84112, USA. g.yan@utah.edu

Journal of pharmaceutical sciences (United States) Dec 2004, 93 (12) p2895-908, ISSN 0022-3549--Print Journal Code: 2985195R

Contract/Grant No.: GM063559; GM; NIGMS

Publishing Model Print

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

Subfile: INDEX MEDICUS

One of the primary safety and tolerability limitations of direct current **iontophoresis** is the potential for electrochemical burns associated with the necessary current densities and/or application times required for effective treatment. **Alternating current** ( **AC** ) transdermal **iontophoresis** has the potential to eliminate electrochemical burns that are frequently observed during direct current transdermal **iontophoresis** . Although it has been demonstrated that the intrinsic permeability of skin can be increased by applying low-to-moderate **AC voltages** , transdermal transport phenomena and enhancement under **AC** conditions have not been systematically studied and are not well understood. The aim of the present work was to study the fundamental transport mechanisms of square-wave **AC iontophoresis** using a synthetic membrane system. The model synthetic

membrane used was a composite Nuclepore membrane. **AC** frequencies ranging from 20 to 1000 Hz and **AC** fields ranging from 0.25 to 0.5 V/membrane were investigated. A charged permeant, tetraethyl ammonium, and a neutral permeant, arabinose, were used. The transport studies showed that flux was enhanced by increasing the **AC voltage** and decreasing **AC** frequency. Two theoretical transport models were developed: one is a homogeneous membrane model; the other is a heterogeneous membrane model. Experimental transport data were compared with computer simulations based on these models. Excellent agreement between model predictions and experimental data was observed when the data were compared with the simulations from the heterogeneous membrane model. (c) 2004 Wiley-Liss, Inc. and the American Pharmacists Association

Descriptors: ***Iontophoresis** --methods--MT; *Membranes, Artificial; *Models, Theoretical; Electric Conductivity; Electrophoresis--methods--MT; Osmosis; Research Support, U.S. Gov't, P.H.S.

Record Date Created: 20041103

Record Date Completed: 20050412

**11/9/3 (Item 3 from file: 155)**

DIALOG(R)File 155:MEDLINE(R)



14261278 PMID: 12695061

**Investigation of properties of human epidermal membrane under constant conductance** alternating current iontophoresis.

Zhu Honggang; Peck Kendall D; **Miller David J** ; Liddell Mark R; Yan Guang ; **Higuchi William I** ; Li S Kevin

Department of Pharmaceutics and Pharmaceutical Chemistry, University of Utah, Salt Lake City, UT 84112, USA.

Journal of controlled release - official journal of the Controlled Release Society (Netherlands) Apr 14 2003, 89 (1) p31-46, ISSN 0168-3659--Print Journal Code: 8607908

Contract/Grant No.: GM063559; GM; NIGMS

Publishing Model Print

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

Subfile: INDEX MEDICUS

Previous studies in our laboratory have shown that enhanced, constant permeant fluxes across human skin can be achieved by applying an **alternating current** ( **AC** ) to maintain skin electrical conductance at a constant level. Relative to conventional direct current (DC) **iontophoresis** , for which current is maintained at a constant level, this newly developed constant conductance **alternating current** (CCAC) method achieves constant fluxes with less inter- and intra-sample variability. The present study focused upon further investigating the permeability properties of human skin during CCAC **iontophoresis** at a variety of target resistance/conductance values. A three-stage experimental protocol was used with flux measurements determined on 3 consecutive days. Stage I was an **AC** only protocol (symmetrical **AC** square-wave signal), stage II was an **AC** plus DC protocol ( **AC** square-wave with DC offset **voltage** ), and stage III was a repeat of stage I. During this three-stage protocol, the skin electrical resistance was maintained at a constant target value by manually adjusting the applied **AC voltage** . Radiolabeled mannitol and urea were model permeants in all experiments. Their fluxes were determined and used

to characterize the permeability properties of human skin. The results from the present study established that: (i) the CCAC protocol made it possible to reduce HEM electrical resistance to different target levels as low as 0.8 kOmega cm(2) and maintain the specific resistance level throughout the flux experiment, (ii) permeant fluxes are proportional to skin electrical conductance, (iii) under the studied CCAC passive conditions, membrane pore size tends to increase as skin resistance decreases, and (iv) as the membrane breaks down, its pore sizes become larger.

Descriptors: *Administration, Cutaneous; *Epidermis--drug effects--DE; *Epidermis--physiology--PH; * **Iontophoresis** --methods--MT; *Skin Physiology--drug effects--DE; Electric Impedance; Humans; Mannitol --pharmacokinetics--PK; Permeability--drug effects--DE; Research Support, U.S. Gov't, P.H.S.; Time Factors; Urea--pharmacokinetics--PK

CAS Registry No.: 57-13-6 (Urea); 69-65-8 (Mannitol)

Record Date Created: 20030415

Record Date Completed: 20040112

**11/9/4 (Item 4 from file: 155)**

DIALOG(R)File 155:MEDLINE(R)



13879692 PMID: 12175741

**Improvement on conventional constant current DC** iontophoresis **: a study using constant conductance** AC iontophoresis.

Zhu Honggang; Li S Kevin; Peck Kendall D; **Miller David J ; Higuchi William I**

30 S 2000 E, Rm 201, Department of Pharmaceutics and Pharmaceutical Chemistry, University of Utah, Salt Lake City, UT 84112, USA. hzhu@m.cc.utah.edu

Journal of controlled release - official journal of the Controlled Release Society (Netherlands) Aug 21 2002, 82 (2-3) p249-61, ISSN 0168-3659--Print Journal Code: 8607908

Contract/Grant No.: 43181; PHS

Publishing Model Print

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

Subfile: INDEX MEDICUS

The purpose of the present study was to compare conventional constant direct current (DC) transdermal **iontophoresis** with a new constant conductance **alternating current** ( **AC** ) **iontophoresis** method. The new method was developed with the intent of reducing flux drift during **iontophoresis** and minimizing skin-to-skin variability. The constant conductance **AC** **iontophoresis** studies involved three electrical components: (1) an initial applied potential used to decrease the human epidermal membrane (HEM) electrical resistance to a target level of either 1.5 or 3.0 k Omega cm(2), (2) an applied 50 Hz square-wave **AC** with a variable potential adjusted to maintain the HEM conductance at the target level during the transport study, and (3) a low **voltage** DC offset of 0 (passive), 0.25, or 0.40 V applied simultaneously with the **AC** to assist permeant transport. Current densities of 0.13 and 0.26 mA/cm(2) were chosen for the conventional constant current DC **iontophoresis** studies. Mannitol was used as the probe permeant for all studies. The constant current DC studies showed significant increases in mannitol flux with time during a given experiment and large skin-to-skin variability. Compared to the

constant current DC experiments, the mannitol flux remained more constant during the constant conductance **AC iontophoresis** and skin-to-skin variability was significantly reduced. On a mechanistic level, changes in the transport properties during constant current DC **iontophoresis** indicate changes in the membrane parameters such as porosity, effective pore size, and/or pore surface charge density during the conventional method of **iontophoresis** . The results from the constant conductance **AC iontophoresis** transport studies imply that this method effectively maintains the membrane parameters that affect transport at a constant state this providing for a relatively constant permanent flux.

Descriptors: *Drug Delivery Systems; *Galvanic Skin Response--physiology --PH; * **Iontophoresis** --methods--MT; *Mannitol--administration and dosage --AD; Biological Transport; Electric Conductivity; Epidermis--metabolism --ME; Humans; Mannitol--pharmacokinetics--PK; Membranes--metabolism--ME; Permeability; Porosity; Research Support, U.S. Gov't, P.H.S.; Time Factors

CAS Registry No.: 69-65-8 (Mannitol)

Record Date Created: 20020814

Record Date Completed: 20021114

**11/9/5 (Item 5 from file: 155)**

DIALOG(R)File 155:MEDLINE(R)



12348826 PMID: 10187752

**Pore induction in human epidermal membrane during low to moderate** voltage iontophoresis **: A study using** AC iontophoresis.

Li S K; Ghanem A H; Peck K D; **Higuchi W I**

Department of Pharmaceutics and Pharmaceutical Chemistry, University of Utah, Salt Lake City, Utah 84112, USA. kevin.li@m.cc.utah.edu

Journal of pharmaceutical sciences (UNITED STATES) Apr 1999, 88 (4) p419-27, ISSN 0022-3549--Print Journal Code: 2985195R

Contract/Grant No.: GM 43181; GM; NIGMS

Publishing Model Print

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

Subfile: INDEX MEDICUS

The present study aimed to investigate new pore induction as a flux-enhancing mechanism in human epidermal membrane (HEM) with low to moderate **voltage** electric fields. The extent of pore induction and the effective pore sizes of these induced pores were to be assessed using a low frequency (12.5 Hz) low to moderate **voltage** (2. 0 to 4.0 V) square-wave **alternating current** ( **ac** ) "passive" permeation method ( **ac iontophoresis** ). This **ac** approach was to allow for inducing and sustaining a state of pore induction in HEM while permitting no significant transport enhancement via electroosmosis; thus, transport enhancement entirely due to new pore induction (enhanced passive permeation) was to be assessed without any contributions from electroosmosis. Good proportionality between the increase in HEM permeability and its electrical conductance was found with the "passive" transport data obtained during square-wave **ac iontophoresis** using urea as the model permeant. Typically, at 3.0 to 4.0 V, HEM conductance increases (and permeability increases) ranged from around 3- to 30-fold. These results appear to be the first direct evidence that new pore induction in HEM is a significant flux enhancing mechanism under moderate **voltage** conditions. The extents of

pore induction in HEM under low frequency moderate **voltage** (2.0 to 3.0 V) **ac** , pulsed direct current (dc), and continuous dc were also compared. The extents of pore induction from square-wave **ac** and pulsed dc were generally of the same order of magnitude but somewhat less than that observed during continuous dc **iontophoresis** at the same applied **voltage** and duration, suggesting less extent of pore induction with reversing polarity or when a brief delay is provided between pulses to allow for membrane depolarization. The average effective pore sizes calculated for the induced pores from the experimental data with urea and mannitol as probe permeants and the hindered transport theory were 12 +/- 2 A, which are of the same order of magnitude as those of preexisting pores determined from conventional passive diffusion experiments.

Descriptors: ***Iontophoresis** --methods--MT; *Skin Absorption; Algorithms; Diffusion; Electric Conductivity; Epidermis--metabolism--ME; Humans; In Vitro; Membranes--metabolism--ME; Research Support, Non-U.S. Gov't; Research Support, U.S. Gov't, P.H.S.

Record Date Created: 19990507

Record Date Completed: 19990507

**11/9/6 (Item 1 from file: 34)**

DIALOG(R)File 34:SciSearch(R) Cited Ref Sci



12018037 Genuine Article#: 722LK Number of References: 36

**Title: In vitro and in vivo comparisons of constant resistance** AC iontophoresis **and DC** iontophoresis

Author(s): Li SK (REPRINT) ; **Higuchi WI** ; Zhu HG; Kern SE; **Miller DJ** ; Hastings MS

Corporate Source: Univ Utah,30 S 2000 E/Salt Lake City//UT/84112 (REPRINT); Univ Utah,Salt Lake City//UT/84112; Aciont Inc,Salt Lake City//UT/84103

Journal: JOURNAL OF CONTROLLED RELEASE, 2003, V91, N3 (SEP 4), P327-343

ISSN: 0168-3659 Publication date: 20030904

Publisher: ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS

Language: English Document Type: ARTICLE

Geographic Location: USA

Journal Subject Category: CHEMISTRY, MULTIDISCIPLINARY; PHARMACOLOGY & PHARMACY

Abstract: A previous in vitro constant electrical resistance **alternating current** ( **AC** ) **iontophoresis** study with human epidermal membrane (HEM) and a model neutral permeant has shown less inter- and intra-sample variability in **iontophoretic** transport relative to conventional constant direct current (DC) **iontophoresis** . The objectives of the present study were to address the following questions. (I) Can the skin electrical resistance be maintained at a constant level by **AC** in humans in vivo? (2) Are the in vitro data with HEM representative of those in vivo? (3) Does constant skin resistance **AC** **iontophoresis** have less inter- and intra-sample variability than conventional constant current DC **iontophoresis** in vivo? (4) What are the electrical and the barrier properties of skin during **iontophoresis** in vivo? In the present study, in vitro HEM experiments were carried out with the constant resistance **AC** and the conventional constant current DC methods using mannitol and glucose as the neutral model permeants. In vivo human experiments were performed using glucose as the permeant with a constant skin resistance **AC** only protocol and two conventional constant current DC methods (continuous constant current DC and constant current DC with its polarity

alternated every 10 min with a 3:7 on:off duty cycle). Constant current DC **iontophoresis** was conducted with commercial constant current DC devices, and constant resistance **AC** **iontophoresis** was carried out by reducing and maintaining the skin resistance at a constant target value with **AC** supplied from a function generator. This study shows that (1) skin electrical resistance can be maintained at a constant level during **AC** **iontophoresis** in vivo; (2) HEM in vitro and human skin in vivo demonstrate similar electrical and barrier properties, and these properties are consistent with our previous findings; (3) there is general qualitative and semi-quantitative agreement between the HEM data in vitro and human skin data in vivo; and (4) constant skin resistance **AC** **iontophoresis** generally provides less interand intra-subject variability than conventional constant current DC. (C) 2003 Elsevier B.V. All rights reserved.

Descriptors--Author Keywords: transdermal ; **iontophoresis** ; constant resistance ; **AC** ; human epidermal membrane ; in vivo/in vitro correlation ; glucose monitoring

Identifiers--KeyWord Plus(R): HUMAN EPIDERMAL MEMBRANE; MODERATE **VOLTAGE** **IONTOPHORESIS** ; CONVECTIVE SOLVENT FLOW; HAIRLESS MOUSE SKIN; REVERSE **IONTOPHORESIS** ; ELECTROOSMOTIC FLOW; **ALTERNATING** - **CURRENT** ; SYNTHETIC MEMBRANE; FLUX ENHANCEMENT; TRANSPORT

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**11/9/7 (Item 2 from file: 34)**
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

10366187 Genuine Article#: 518PE Number of References: 26
**Title: Human epidermal membrane constant conductance** iontophoresis : alternating current **to obtain reproducible enhanced permeation and reduced lag times of a nonionic polar permeant**
Author(s): Song Y; Li SK; Peck KD; Zhu HG; Ghanem AH; **Higuchi WI (REPRINT)**
Corporate Source: Univ Utah,Dept Pharmaceut & Pharmaceut Chem,30 S 2000 E,Rm 213/Salt Lake City//UT/84112 (REPRINT); Univ Utah,Dept Pharmaceut & Pharmaceut Chem,Salt Lake City//UT/84112; Brigham Young Univ,Dept Chem,Rexburg//ID/83460
Journal: INTERNATIONAL JOURNAL OF PHARMACEUTICS, 2002, V232, N1-2 (JAN 31) , P45-57
ISSN: 0378-5173 Publication date: 20020131
Publisher: ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS
Language: English Document Type: ARTICLE
Geographic Location: USA
Journal Subject Category: PHARMACOLOGY & PHARMACY
Abstract: An experimental protocol, using an initial 1 min direct current (DC) applied potential of 4 V followed by **alternating current** ( **AC** ), was established to: (a) increase conductance and permeability and decrease lag time for human epidermal membrane (HEM) relative to unaltered HEM and; (b) maintain constant conductance and permeability during flux studies. The protocol allowed specific permeation parameters of the membrane to be characterized under electrically enhanced. constant flux conditions. The permeability, lag time, and effective membrane thickness were determined using a nonionic polar permeant. urea. while the enhanced conductance was maintained at a constant level with **AC** . A tortuous pore pathway model was employed to analyze the data. The **AC** protocol increased membrane permeability. and decreased lag time and effective membrane thickness relative to similar parameters obtained in previous studies from unaltered HEM. Lag times ranged from 32.0 to 105.5 min, and permeability coefficients calculated from steady state fluxes ranged from 1.68 to 6.03 x 10(-7) cm/s for HEM samples with electrical resistance values during transport of 2.3-8.0 kOmega cm(2). Effective membrane thicknesses were calculated to range from 0.34 to 0.61 cm during **AC iontophoresis** . Significant additional results were obtained when the protocol was applied for two consecutive runs using the same HEM sample, with time for the HEM sample to recover between runs. During the second run, the applied potential was adjusted to reproduce the conductance obtained on the first run. Under these conditions, the consecutive runs yielded essentially the same lag time, permeability and effective membrane thickness values. These results suggest that constant fluxes can be achieved by keeping HEM electrical conductance constant during **AC iontophoresis** . (C) 2002 Elsevier Science B.V. All rights reserved.
Descriptors--Author Keywords: transdermal ; **iontophoresis** ; constant conductance ; permeation ; human epidermal membranes ; lag time
Identifiers--KeyWord Plus(R): MODERATE **VOLTAGE IONTOPHORESIS** ; SKIN; ELECTROPORATION; TRANSPORT; DELIVERY; GLUCOSE; INTACT

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**[The following were found during the non-inventor search:]**

L25 ANSWER 7 OF 11 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:786460 HCAPLUS <<LOGINID::20060707>>
DOCUMENT NUMBER: 128:11564
TITLE: Characterization of the Transport Pathways Induced during Low to Moderate ***Voltage*** ***Iontophoresis*** in Human Epidermal Membrane
AUTHOR(S): Li, S. Kevin; Ghanem, Abdel-Halim; Peck, Kendall D.; Higuchi, William I.
CORPORATE SOURCE: Department of Pharmaceutics and Pharmaceutical Chemistry, University of Utah, Salt Lake City, UT, 84112, USA
SOURCE: Journal of Pharmaceutical Sciences (1998), 87(1), 40-48
CODEN: JPMSAE; ISSN: 0022-3549
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB This report describes the results of ***iontophoresis*** expts. involving the transport of polar nonelectrolytes across human epidermal membrane (HEM) at a moderate applied ***voltage*** of 2.0 ***V*** and where the data are interpreted via a convective transport model and hindered transport theory. A principal finding is that although HEM ***iontophoresis*** at 2.0 ***V*** resulted in a large increase in HEM porosity, the pore radii of the newly induced pores in HEM as calcd. from the ***iontophoresis*** data using the hindered transport theory were found to be in the range of 6-12 .ANG.. This supports the view that electroporation at these modest applied **voltages** results in pores with sizes the same order of magnitude but somewhat smaller than those estd. for the preexisting pores in HEM prior to electroporation. This outcome is also important from a practical standpoint, as flux enhancement for large mols. (such as oligonucleotides and polypeptides) arising from electroporation under these conditions would be expected to be significantly less than if the resulting pore sizes were much greater. Providing a "prepulse" of 4.0, 8.0, and 15 ***V*** prior to the 2.0 ***V*** ***iontophoresis*** generally gave greater increases in HEM conductance (and, therefore, in porosity) but did not significantly **change** the deduced effective pore radii (around 5-9 .ANG.). The **alter**ation during and the recovery of HEM after ***iontophoresis*** was also investigated. The recovery behavior was found to be dependent upon both the duration of the applied ***voltage*** and the magnitude of its effects: the recovery for a HEM sample that experienced a large increase in elec. conductance during ***iontophoresis*** was generally poorer than that for a sample that was more resistant to the elec. field. Incomplete recovery was generally obsd. in expts. with long ***iontophoresis*** duration (50 ***min*** ) and with the higher **voltages** (4.0, 8.0 ***V*** , and 15 ***V*** ). In these cases, the **barrier** properties of HEM were more greatly **altered** as indicated by larger increases in the elec. conductance and passive ***permeability*** of HEM after ***iontophoresis*** .

**L25 ANSWER 10 OF 11 HCAPLUS COPYRIGHT 2006 ACS on STN**
ACCESSION NUMBER: 1994:307349 HCAPLUS <<LOGINID::20060707>>
DOCUMENT NUMBER: 120:307349

**TITLE:** **Studies on the effects of applied ***voltage*** and duration on human epidermal membrane alteration/recovery and the resultant effects upon ***iontophoresis***

AUTHOR(S): Inada, Hirohiko; Ghanem, Abdel Halim; **Higuchi, William I.**

CORPORATE SOURCE: Coll. Pharm., Univ. Utah, Salt Lake City, UT, 84112, USA

SOURCE: Pharmaceutical Research (1994), 11(5), 687-97
CODEN: PHREEB; ISSN: 0724-8741

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The effects of applied ***voltage*** and the duration of application upon human epidermal membrane (HEM) **alter**ations and recovery were investigated. All expts. were conducted using a two-chamber diffusion cell with const. DC ***voltage*** (250-4000 mV) applied over a predetd. period, and HEM **change**s were monitored by measuring the elec. resistance before and after ***voltage*** termination. The key findings were that the rate of decrease in resistance was strongly dependent upon the applied ***voltage*** , the reversible recovery times were dependent upon both the magnitude and the duration of the applied field (frequently were several orders of magnitude greater than times for attaining significant resistance redn.), and reversible recovery times were much longer when lower **voltage**s were applied for longer times to attain the same decrease in elec. resistance than for higher **voltage**s at shorter times. These findings closely parallel those obtained on elec. breakdown/recovery of bilayer membranes (electroporation). The second part of this work examd. the hypothesis that decreases in HEM elec. resistance induced by the applied ***voltage*** are accompanied by proportional increases in HEM ***permeability*** . A study was designed to test this hypothesis involving a four-stage protocol with HEM: passive transport, 250-mV ***iontophoresis*** , 2000-mV ***iontophoresis*** for 10 ***min*** , then back to 250-mV ***iontophoresis*** . The data obtained strongly support the view that the HEM **alter**ations induced by the elec. field result in pore formation and in the expected **change**s in HEM ***permeability*** .

**35/7/8 (Item 8 from file: 155)**
DIALOG(R)File 155:MEDLINE(R)
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10133157 PMID: 8058638

**Studies on the effects of applied voltage and duration on human epidermal membrane alteration/recovery and the resultant effects upon iontophoresis.**

Inada H; Ghanem A H; Higuchi W I

Department of Pharmaceutics, College of Pharmacy, University of Utah, Salt Lake City 84112.

Pharmaceutical research (UNITED STATES) May 1994, 11 (5) p687-97, ISSN 0724-8741--Print Journal Code: 8406521

Contract/Grant No.: GM 43181; GM; NIGMS

Publishing Model Print

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

The effects of applied **voltage** and the duration of application upon human epidermal membrane (HEM) **alter**ations and recovery were investigated. All experiments were conducted using a two-chamber diffusion cell with constant DC **voltage** (250-4000 mV) applied over a predetermined period, and HEM **changes** were monitored by measuring the electrical resistance before and after **voltage** termination. The key findings were that the rate of decrease in resistance was strongly dependent upon the applied **voltage** , the reversible recovery times were dependent upon both the magnitude and the duration of the applied field (frequently were several orders of magnitude greater than times for attaining significant resistance reduction), and reversible recovery times were much longer when lower **voltages** were applied for longer times to attain the same decrease in electrical resistance than for higher **voltages** at short times. These findings closely parallel those obtained on electrical breakdown/recovery of bilayer membranes (electroporation). The second part of this work examined the hypothesis that decreases in HEM electrical resistance induced by the applied **voltage** are accompanied by proportional increases in HEM **permeability**. A study was designed to test this hypothesis involving a four-stage protocol with HEM: passive transport, 250-mV **iontophoresis** , 2000-mV **iontophoresis** for 10 **min** , then back to 250-mV **iontophoresis** . The data obtained strongly support the view that the HEM **alter**ations induced by the electric field result in pore formation and in the expected **changes** in HEM **permeability.**

Record Date Created: 19940912
Record Date Completed: 19940912

**35/7/23 (Item 23 from file: 155)**
DIALOG(R)File 155:MEDLINE(R)

11671937 PMID: 9452966

**Characterization of the transport pathways induced during low to moderate voltage iontophoresis in human epidermal membrane.**

Li S K; Ghanem A H; Peck K D; Higuchi W I
Department of Pharmaceutics and Pharmaceutical Chemistry, University of Utah, Salt Lake City 84112, USA.

Journal of pharmaceutical sciences (UNITED STATES) Jan 1998, 87 (1) p40-8, ISSN 0022-3549--Print Journal Code: 2985195R
Contract/Grant No.: GM 43181; GM; NIGMS
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

This report describes the results of **iontophoresis** experiments involving the transport of polar nonelectrolytes across human epidermal membrane (HEM) at a moderate applied **voltage** of 2.0 **V** and where the data are interpreted via a convective transport model and hindered transport theory. A principal finding is that although HEM **iontophoresis** at 2.0 **V** resulted in a large increase in HEM porosity, the pore radii of the newly induced pores in HEM as calculated from the **iontophoresis** data using the hindered transport theory were found to be in the range of 6-12 A. This supports the view that electroporation at these modest applied **voltages** results in pores with sizes the same order of magnitude but somewhat smaller than those estimated for the preexisting pores in HEM prior to electroporation. This outcome is also important from a practical

standpoint, as flux **enhance**ment for large molecules (such as oligonucleotides and polypeptides) arising from electroporation under these conditions would be expected to be significantly less than if the resulting pore sizes were much greater. Providing a "prepulse" of 4.0, 8.0, and 15 **V** prior to the 2.0 **V** **iontophoresis** generally gave greater increases in HEM conductance (and, therefore, in porosity) but did not significantly **change** the deduced effective pore radii (around 5-9 A). The **alter**ation during and the recovery of HEM after **iontophoresis** was also investigated. The recovery behavior was found to be dependent upon both the duration of the applied **voltage** and the magnitude of its effects: the recovery for a HEM sample that experienced a large increase in electrical conductance during **iontophoresis** was generally poorer than that for a sample that was more resistant to the electric field. Incomplete recovery was generally observed in experiments with long **iontophoresis** duration (50 **min** ) and with the higher **voltages** (4.0, 8.0 **V** , and 15 **V** ). In these cases, the **barrier** properties of HEM were more greatly **alter**ed as indicated by larger increases in the electrical conductance and passive **permeab**ility of HEM after **iontophoresis.**

Record Date Created: 19980226
Record Date Completed: 19980226

**25/7/4 (Item 4 from file: 285)**
DIALOG(R)File 285:BioBusiness(R)

00623998
**Studies on the effects of applied voltage and duration on human epidermal membrane alteration-recovery and the resultant effects upon iontophores**is.
Inada H; Ghanem A-H; Higuchi W I
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ABSTRACT: The effects of applied **voltage** and the duration of application upon human epidermal membrane (HEM) **alter**ations and recovery were investigated. All experiments were conducted using a two-chamber diffusion cell with constant DC **voltage** (250-4000 mV) applied over a predetermined period, and HEM **change**s were monitored by measuring the electrical resistance before and after **voltage** termination. The key findings were that the rate of decrease in resistance was strongly dependent upon the applied **voltage** , the reversible recovery times were dependent upon both the magnitude and the duration of the applied field (frequently were several orders of magnitude greater than times for attaining significant resistance reduction), and reversible recovery times were much longer when lower **voltages** were applied for longer times to attain the same decrease in electrical resistance than for higher **voltages** at short times. These findings closely parallel those obtained on electrical breakdown/recovery of bilayer membranes (electroporation). The second part of this work examined the hypothesis that decreases in HEM electrical resistance induced by the applied **voltage** are accompanied by proportional increases in HEM **permeability** . A study was designed to test this hypothesis involving a four-stage protocol with HEM: passive transport, 250-mV **iontophoresis** , 2000-mV **iontophoresis** for 10 **min** , then back to 250-mV **iontophoresis** . The data obtained strongly support the view that the HEM **alter**ations induced by the electric field result in pore formation and in the expected **change**s in HEM **permeability.**